Background Document for Meeting of Advisory Committee for Reproductive Health Drugs
March 4, 2013

NDA 22-506

Gabapentin tablets 600 mg

(Proposed trade name: Sefelsa)

Depomed, Inc.

Proposed Indication:

Treatment of moderate to severe vasomotor symptoms (VMS) due to menopause

Proposed Dosing Regimen:

Titrate to a total daily dose of 1800 mg, taken orally as 600 mg with the morning meal and 1200 mg with the evening meal

Prepared by the Division of Reproductive and Urologic Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

February 4, 2013

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought NDA 22-506 to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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List of Abbreviations and Definitions

AE	Adverse Event
ANCOVA	Analysis of covariance
AUC	Area under the curve
BMI	Body mass index
C-SSRS	Columbia Suicide Severity Rating Scale
Cmax	Maximum concentration
CSR	Complete Study Report
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DVT	Deep vein thrombosis
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
HLT	Higher level terms
IND	Investigational New Drug Application
ISS	Integrated Summary of Safety
ITT	Intent to Treat
LOCF	Last observation carried forward
LS	Least squares
MI	myocardial infarction
MMRM	Mixed model repeated measure
NDA	New Drug Application
PE	Pulmonary embolism
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic
RD	Risk difference
ROC	Receiver Operating Characteristic
SAE	Serious adverse event
SMQ	Standardized MedDRA Query
SOC	System organ class
SPA	Special Protocol Assessment
US	United States
VMS	Vasomotor symptoms

DRAFT TOPICS FOR DISCUSSION

Committee members are asked to reflect upon the following issues as they review the information provided in this Background Document.

Issues for discussion include the following:

- Based on the Applicant's pre-specified analyses, is there sufficient evidence to conclude that gabapentin is effective in treating moderate to severe vasomotor symptoms (VMS) due to menopause?
- Is the overall risk/benefit profile of gabapentin acceptable to support approval of this product for the proposed indication?

1. Background

1.1 Objective of Meeting and Overview of Development Program

The purpose of this Advisory Committee meeting is to review and discuss the efficacy, safety and overall risk/benefit profile of gabapentin tablets, indicated for the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause. This NDA is brought to the Advisory Committee because, if approved, it would potentially be the first and only nonhormonal product approved for treatment of VMS. In addition, according to the Applicant's pre-specified efficacy analyses, all three of the phase 3 studies failed to meet the required statistical level of significance on the reduction of VMS frequency from baseline to Week 12, and one study failed to meet the required statistical level of significance on the reduction of VMS severity from baseline to Week 12. Finally, as with any drug, the overall risk/benefit profile of the product for the requested indication must be assessed.

The primary sources of the clinical efficacy and safety data in support of approval of gabapentin for this indication are three randomized, double-blind, placebo-controlled multicenter phase 3 clinical trials conducted entirely in the US (Study 81-0058, hereafter referred to as Study 58; Study 81-0059, hereafter referred to as Study 59; and Study 81-0064, hereafter referred to as Study 64).

1.2 Description of Product

Gabapentin was first marketed commercially in the US in 1993 as a capsule under the brand name Neurontin; subsequently Neurontin has been approved in tablet and oral solution formulations. Approved indications for Neurontin are for postherpetic neuralgia and epilepsy. A prodrug of gabapentin, gabapentin enacarbil, was approved in 2011 under the brand name Horizant, with indications for restless leg syndrome and postherpetic neuralgia. Currently, gabapentin is also used off-label for treatment of VMS.

A tablet formulation of gabapentin is proposed for marketing in this NDA. This formulation is currently marketed as Gralise (NDA 022544, approved in 2011) for the management of postherpetic neuralgia, dosed as 1800 mg once daily with the evening meal. Labeling for all gabapentin products warns against interchanging the specific products because of differing pharmacokinetic (PK) profiles.

Current Gralise labeling is included in Appendix 1. Important issues described in labeling include:

- A warning about risk of suicidality (class labeling for antiepileptic drugs)
- Need for gradual withdrawal over a week or longer
- Tumorigenic potential as demonstrated in nonclinical studies (pancreatic acinar adenocarcinoma in male rats only), along with lack of information in humans on the effect of gabapentin on the incidence of new tumors or the worsening or recurrence of previously diagnosed tumors

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and multiorgan hypersensitivity, a potentially fatal condition that has been observed in patients taking antiepileptic drugs including Gralise

Gabapentin has not been approved in any country for treatment of VMS.

1.3 Treatment of Vasomotor Symptoms

VMS, or hot flushes/flashes, are symptoms of warmth and sweating that are very common (occurring in up to 75% of women) in the menopausal transition. Moderate VMS is defined as a sensation of heat with sweating that does not disrupt the woman's activities, while severe VMS is defined as a sensation of heat with sweating that causes transient cessation of activities. While VMS can be very bothersome, causing discomfort, embarrassment, and disruption of sleep, it is not a life-threatening condition. VMS may persist up to five years, or even longer in a minority of women, but is ultimately a self-limited condition.

While there are a variety of drug products in different formulations (tablet, transdermal system, vaginal ring) approved for treatment of menopausal symptoms (including both VMS and symptoms related to vulvar and vaginal atrophy), all contain either estrogen alone or estrogen plus a progestin. The estrogen-only products carry a Boxed Warning about the risk of endometrial cancer in a woman with a uterus who uses unopposed estrogen; this risk is mitigated by addition of a progestin. The estrogen and estrogen/progestin products have a Boxed Warning describing findings from the Women's Health Initiative that reported increased risks of stroke, myocardial infarction (MI; associated only with use of estrogen/progestin), deep vein thrombosis (DVT), pulmonary embolism (PE; associated only with use of estrogen/progestin), invasive breast cancer (associated only with use of estrogen/progestin) and probable dementia in women $\geq$ 65 years old. Both estrogen-alone and estrogen/progestin products are contraindicated in women with known, suspected, or history of breast cancer. Other contraindications include other known or suspected estrogen-dependent neoplasia, active or history of DVT or PE, active or history of arterial thromboembolic disease (such as stroke or MI), known liver dysfunction or disease and known thrombophilic disorders. Therefore, there are significant subgroups of women, particularly those with current or a history of breast cancer, who may be symptomatic during menopause but unable to use the hormonal preparations.

Many other products are used off-label to treat VMS, including antidepressants, herbal and soy products; however, rigorous evidence of the safety and efficacy of such treatments is lacking.

Gabapentin, the focus of this Advisory Committee meeting, if approved, would potentially be the first and only nonhormonal product approved for treatment of VMS.

1.4 Regulatory Guidance for the Development of Gabapentin for VMS

The FDA issued a draft guidance for clinical evaluation of hormonal products for menopausal symptoms in 2003 (See Appendix 2), and has generally provided advice based on this guidance for both hormonal and nonhormonal products intended to treat VMS. This document states that the VMS indication is to treat "moderate to severe

vasomotor symptoms associated with the menopause." Clinical definitions of mild, moderate and severe VMS are provided, with moderate hot flushes defined as "sensation of heat with sweating, able to continue activity" and severe hot flushes defined as "sensation of heat with sweating, causing cessation of activity." Recommended entry criteria include postmenopausal women (defined as 12 months of spontaneous amenorrhea, 6 months of spontaneous amenorrhea with serum FSH > 40 mIU/mL, or six weeks post-surgical bilateral oophorectomy) who have a minimum of 7-8 moderate to severe hot flushes per day or 50-60 per week at baseline. Four co-primary endpoints are recommended:

- Mean change from baseline in frequency of moderate to severe hot flushes at Week 4
- Mean change from baseline in frequency of moderate to severe hot flushes at Week 12
- Mean change from baseline in severity of moderate to severe hot flushes at Week 4
- Mean change from baseline in severity of moderate to severe hot flushes at Week 12

The primary efficacy analyses are intended to show a clinically and statistically significant reduction of both frequency and severity at Week 4 that is maintained at Week 12. Daily diary entries can be used as the basis of the co-primary endpoints.

The formulation of gabapentin that is the subject of this NDA was studied under IND 76,625. A preIND meeting was held in February 2007. The FDA recommended two adequate and well-controlled studies and noted that the proposed phase 2 dose-finding study would not serve as one of these, in part because the efficacy endpoints differed from those recommended in the 2003 draft Guidance. The FDA requested evaluation of the persistence of benefit at 24 weeks, although this did not need to be a co-primary endpoint.

The Applicant and FDA met again in June 2008 to discuss the phase 3 program. FDA reiterated its request for six month safety and efficacy data and the Applicant agreed to conduct one three-month and one six-month study. FDA recommended that persistence of benefit rely on observed data and not imputed data.

Following completion of Studies 58 and 59, the Applicant met with FDA in December 2009; this had initially been requested as a preNDA meeting, but after review of the meeting package, which acknowledged that the studies had failed to meet the requisite efficacy endpoints, FDA reclassified it as a guidance meeting. The Applicant noted a high placebo response in the two completed studies, and planned to minimize the placebo response in a third clinical trial by requiring a two week run-in period to provide for more stable baseline data. FDA requested the Applicant to evaluate the potential for suicidality in the new trial. FDA also noted that, given the failure to show a statistical benefit at Week 24 in Study 58, the new study should evaluate persistence of benefit in VMS frequency at six months as well as the co-primary endpoints of VMS frequency and severity at Weeks 4 and 12. In addition, because the completed trials showed a placebo-corrected reduction of VMS frequency that was well below two hot flushes per day, the Applicant was asked to demonstrate the clinical meaningfulness of the change in VMS frequency in the new trial. The FDA provided guidance on the use of an anchoring

global satisfaction questionnaire to determine a cutoff value that indicates satisfaction with treatment, followed by a responder analysis. The Applicant proposed to use a nonparametric analysis for the co-primary endpoints in the new study; this was acceptable to FDA although an ANCOVA model was requested as a supportive analysis. FDA agreed with the Applicant's plan to evaluate only the 1800 mg dose in the new study.

A Special Protocol Assessment (SPA) was requested for this new study (Study 64), and the FDA provided a No Agreement letter in March 2010. Areas of disagreement included the plan for assessment of suicidality, the need to pre-specify persistence of benefit in VMS frequency at 24 weeks as a key secondary endpoint, and the proposed methodology for determining clinical meaningfulness. The Applicant was also advised that the NDA submission should report the protocol-specified analyses for all phase 3 studies; the plan to submit nonparametric analyses for all three studies was not appropriate. The pre-specified nonparametric analysis was acceptable for Study 64, but the study reports for the other two already-completed studies should present the pre-specified ANCOVA analyses and include nonparametric analyses only as sensitivity analyses.

An SPA submission of the revised Study 64 protocol again received a No Agreement in April 2010, due to disagreements about excluding subjects with missing global satisfaction scores and need for clarification of the logistic regression model used for the clinical meaningfulness assessment. A follow-up meeting was held in June 2010, where the Applicant discussed planned revisions to address the FDA comments on the protocol. An SPA was submitted again and an Agreement letter was issued in August 2010.

A preNDA meeting was held in April 2012. The Applicant discussed a plan to provide both the nonparametric and ANCOVA analyses for each of the studies. The Applicant noted that Studies 58 and 59 used an ANCOVA analysis which relies upon normally distributed data, but this assumption was not met. Based on this finding, a nonparametric analysis was pre-specified for Study 64. The FDA indicated that efficacy results should be provided according to the protocol-specified analysis, but that sensitivity analyses could also be presented. The Applicant was advised that, given the mixed efficacy results, which appear to be dependent upon the analysis method used, it was likely that the NDA would be discussed at an Advisory Committee meeting. FDA also stated that any integrated summary of efficacy would be considered supportive; the efficacy evaluation would be based on separate results from each of the individual studies.

2. Clinical Development of Gabapentin

2.1 Overview of Product Development

The development program for gabapentin for the VMS indication consisted of six phase 1 bioavailability studies, a phase 2 dose-finding study and three phase 3 randomized clinical trials in postmenopausal women. An overview of the phase 2 and 3 clinical studies is presented in Table 1.

Table 1 Phase 2 and 3 Studies for Gabapentin for VMS

Study # and objective	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	N, Enrolled (Completed)	Population	Duration of Treatment
Phase 2					
81-0056 PK/ PD	Multicenter, Randomized Double-Blind, Placebo-Controlled, Dose Escalation	Placebo 3 gabapentin doses: After final titration: A: 600 mg AM; 1200 mg PM B: 600 mg AM; 1800 mg PM C: 1200 mg AM; 1800 mg PM	124 (107) Gabapentin 1800 mg – 30 Gabapentin 2400 mg - 30 Gabapentin 3000 mg - 32 Placebo - 30	Post-menopausal women	12 weeks (two 6-week treatment periods) plus a 1 week taper period
Phase 3					
81-0058 Safety & Efficacy	Multicenter, Randomized Double-Blind, Placebo-Controlled	Placebo Gabapentin 1800 mg After titration: 600 mg AM; 1200 mg PM Gabapentin 1200 mg	541 (373) Gabapentin 1200 mg - 178 Gabapentin 1800 mg – 182 Placebo - 181	Post-menopausal women	25 weeks (1 week titration; 24 weeks stable treatment)
81-0059 Safety & Efficacy	Multicenter, Randomized Double-Blind, Placebo-Controlled	Placebo Gabapentin 1800 mg After titration: 600 mg AM; 1200 mg PM Gabapentin 1200 mg	565 (446) Gabapentin 1200 mg - 192 Gabapentin 1800 mg – 190 Placebo - 183	Post-menopausal women	13 weeks (1 week titration; 12 weeks stable treatment)
81-0064 Safety & Efficacy	Multicenter, Randomized Double-Blind, Placebo-Controlled	Placebo Gabapentin 1800 After titration: 600 mg AM; 1200 mg PM	600 (397) Gabapentin 1800 mg - 302 Placebo - 298	Post-menopausal women	24 weeks (1 week titration; 23 weeks stable treatment)

Source: Modified from the Applicant's Integrated Summary of Safety (ISS), table 1, pp12-13 and Complete Study Reports (CSRs) for Study 58, Table 14.1.3; Study 59, Table 14.1.3; Study 64, Table 14.1.3.

2.2 Overview of Pharmacology and Toxicology

Gabapentin is a synthetic analog of gamma-aminobutyric acid (GABA). However, it does not interact with either GABA-A (ionotropic) or GABA-B (metabotropic) receptors. It is known to bind to the α2δ subunit of voltage-dependent calcium channels, which are widely expressed in nerve and muscle cells. However, because the physiological basis of VMS due to menopause has not been established, the mechanism of action of gabapentin in potentially regulating VMS is not known.

No nonclinical studies were conducted to assess the pharmacodynamics of gabapentin for treatment of vasomotor symptoms, which is difficult to model in nonclinical species. To support this new indication, the Applicant is cross-referencing approved NDA 22-544 (Gralise) for nonclinical toxicity testing of the drug product.

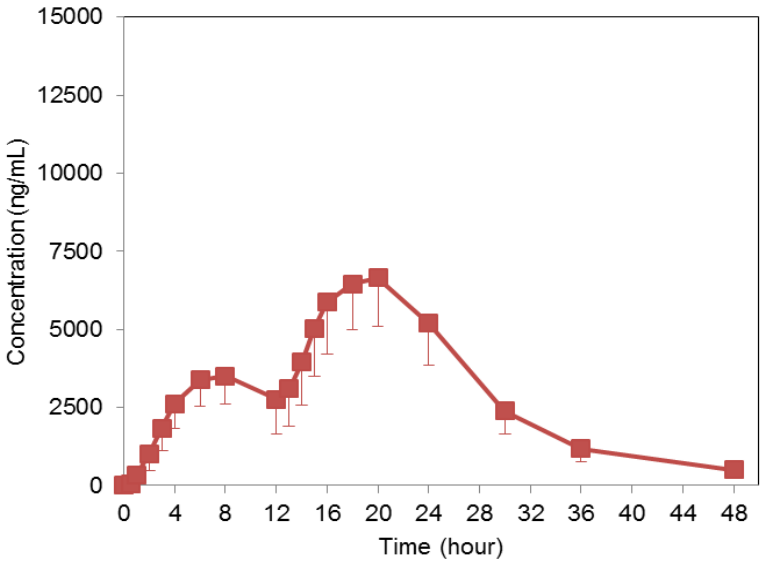
2.3 Overview of Clinical Pharmacology

The mechanism of action of gabapentin with respect to treatment of VMS is unknown.

Gabapentin is absorbed from the proximal small bowel by a saturable L-amino transport system. Gabapentin bioavailability decreases as the dose is increased. The saturable transporter is reportedly responsible for the less-than-dose-proportional increase in gabapentin exposure with increasing doses.

Food increases the extent of absorption. Exposure, as measured by area under the curve (AUC) and maximum concentration (Cmax) of gabapentin, increases with an increase in fat content of meals. A meal containing 30% fat increases the AUC and Cmax by 33% each. A meal containing 50% fat increases the AUC and Cmax by 118% and 84%, respectively.

Figure 1 Single Dose PK: Mean (±SD) Gabapentin Concentration (600 mg AM + 1200 mg PM)



After multiple dosing, there was minimal (less than 10%) accumulation of gabapentin. Gabapentin is eliminated by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans.

The drug elimination half-life is approximately 5-7 hours. The renal clearance of gabapentin is proportional to creatinine clearance. In elderly patients and patients with impaired renal function, plasma clearance is reduced. Therefore, dosage adjustment is needed in patients with renal impairment.

2.4 Overview of Clinical Studies

The clinical portion of the NDA focuses on review of the three phase 3 studies. Study 58 was a study in postmenopausal women aged 18-70 years with at least seven moderate to severe daily hot flushes that compared gabapentin 1800 mg, gabapentin 1200 mg and placebo, and evaluated persistence of benefit in VMS frequency at 24 weeks of treatment as well as the co-primary efficacy endpoints of VMS frequency and severity at Weeks 4 and 12 (following a one-week titration). Study 59 enrolled a similar population and

evaluated the same three treatment arms over a 13-week period that included a one-week titration and a 12-week stable dosing period. Study 64 studied the same population but evaluated only the 1800 mg gabapentin dose vs. placebo at Weeks 4, 12 and 24; a slower one week titration was considered part of the treatment period in this study.

A total of 1,706 subjects were randomized in the phase 3 trials, 370 were randomized to receive gabapentin 1200 mg/day, 674 were randomized to receive gabapentin 1800 mg/day, and 662 were randomized to receive placebo.

2.5 Basis for Dose Selection

Dose selection was based on Study 81-0056, a phase 2 study that evaluated 124 symptomatic postmenopausal women over 12 weeks. The study consisted of two five-week treatment periods (each treatment period was preceded by a one-week titration period to achieve the assigned dose). Patients were randomized to one of the following treatment arms:

- placebo
- 600 mg PM (Weeks 2-6) then 600 mg AM + 1200 mg PM (Weeks 8-12)
- 600 mg twice daily (Weeks 2-6) then 600 mg AM + 1800 mg PM (Weeks 8-12)
- 1200 mg PM (Weeks 2-6) then 1200 mg AM + 1800 mg PM (Weeks 8-12)

At the end of treatment (or early termination), subjects had one week of dose tapering. The primary analyses were the mean change in average daily frequency and severity score of moderate to severe hot flashes from baseline to the final week of the treatment period. The results, based on daily diaries showed efficacy for the 1800 mg and 2400 mg doses but not for the 3000 mg dose. There did not appear to be an added benefit using the 2400 mg dose over the 1800 mg dose, and reported adverse effects were higher at the 2400 mg and 3000 mg doses. However, subject- and clinician-reported Global Impression of Change instruments indicated some efficacy for the 1200 mg dose at Week 6, so the Applicant evaluated both 1200 mg and 1800 mg in phase 3.

3. Objectives and Design of Phase 3 Trials

The efficacy of gabapentin 1800 mg was evaluated in three phase 3 trials (Studies 58, 59, and 64). All three studies were randomized, placebo-controlled, double-blind, multicenter, and parallel-arm studies conducted in the US. Studies 58 and 59 had three treatment arms (gabapentin 1200 mg and 1800 mg, and placebo), and Study 64 had two treatment arms (gabapentin 1800 mg and placebo).

A total of 541 subjects across 47 sites in Study 58, 564 subjects across 44 sites in Study 59, and 600 subjects across 67 sites in Study 64 were enrolled.

3.1 Study Objectives

Primary Objective

The primary objective of the trials was to assess the efficacy of gabapentin for treatment of VMS due to menopause at Weeks 4 and 12. Assessment of a number of safety parameters was the safety objective.

Secondary Objectives

Among the Applicant's secondary objectives was to assess the change from baseline in the frequency and severity of moderate to severe hot flushes at Week 24 (in Studies 58 and 64).

FDA Comments

- **The primary and secondary objectives were consistent with FDA guidance.**
- **In Study 64, an evaluation of clinically meaningful improvement in VMS frequency was specified using a discriminant analysis; but it was not listed as a secondary objective. FDA considered it a supportive analysis.**

3.2 Overall Study Design and Conduct

All three phase 3 studies were randomized, double-blind, placebo-controlled, multicenter studies in women with either natural or surgical menopause aged 18-70 years with ≥ 7 moderate-to-severe hot flushes per day for at least 30 days prior to enrollment. These trials were conducted entirely in the US.

Studies 58 and 59 had treatment weeks counted from the end of the first week (titration week after randomization), and Study 64 had treatment weeks counted immediately after randomization (including the titration week).

3.2.1 Study Schedule and Conduct

The Schedule of Events is displayed in Appendix 3. After a screening period of up to four weeks, subjects in these studies were treated with gabapentin 1800 mg, gabapentin 1200 mg (Studies 58 and 59 only) or placebo during a double-blind period of at least 12 weeks for the primary efficacy evaluation. Subjects received therapy for up to six months in Studies 58 and 64. All studies used a titration regimen (see Table 2 and Table 3) during the first week on-treatment, although the regimen differed somewhat in Study 64. In Studies 58 and 59, the titration week was not counted as part of the treatment period (i.e., the efficacy evaluations at Weeks 4 and 12 were actually conducted at Weeks 5 and 13 after initial dosing), while Study 64 evaluated subjects at Weeks 4 and 12 after the initial dosing, including the week of titration as on-treatment.

Following completion of the baseline period, subjects who were compliant with diary entry and dosing and who continued to meet hot flush eligibility criteria (i.e., having more than 7 moderate to severe hot flushes per day or ≥ 50 moderate to severe hot flushes per week) were randomized into the double-blind treatment period. In Studies 58 and 59, randomization was in a 1:1:1 ratio to gabapentin 1200 mg, gabapentin 1800 mg or placebo. In Study 64, randomization was in a 1:1 ratio to gabapentin 1800 mg or placebo. Gabapentin 1800 mg was dosed orally as one 600 mg tablet with the morning meal, and two 600 mg tablets with the evening meal. The total treatment duration was 25 weeks in Study 58, 13 weeks in Study 59, and 24 weeks in Study 64.

Table 2 Titration Schedule in Studies 58 and 59

	Study Day	1200 mg (1200 mg PM)	1800 mg (600 mg AM and 1200 mg PM)	Placebo
No Adverse Event	Day 1, 2	none/600 mg	none/600 mg	none/0 mg
	Day 3, 4, 5	none/1200 mg	none/1200 mg	none/0 mg
	Day 6, 7	0 mg/1200 mg	600 mg/1200 mg	0 mg/0 mg
With Adverse Event	Day 1, 2, 3	none/600 mg	none/600 mg	none/0 mg
	Day 4, 5, 6, 7	none/1200 mg	none/1200 mg	none/0 mg

Source: CSRs for Studies 58 and 59, Text Tables 9-1 and 9-2

Table 3 Titration Schedule in Study 64

	Study Day	1800 mg (600 mg AM and 1200 mg PM)	Placebo
No Adverse Event	Day 1, 2, 3	none/600 mg	none/0 mg
	Day 4, 5, 6	none/1200 mg	none/0 mg
	Day 7	600 mg/1200 mg	0 mg/0 mg
With Adverse Event	Day 1, 2, 3, 4, 5, 6	none/600 mg	none/0 mg
	Day 7, 8, 9, 10, 11, 12	none/1200 mg	none/0 mg
	Day 13	600 mg/1200 mg	0 mg/0 mg

Source: CSRs for Studies 58 and 59, Text Tables 9-1 and 9-2 in the clinical study report

Daily Diaries

The phase 2 study and both phase 3 studies used an electronic diary, a handheld electronic device that was used throughout the study to allow subjects to record the occurrence and severity of each hot flush event in real time for daily entry of hot flush data. Subjects also had the opportunity to add any unrecorded events each morning to capture events that may have happened during the night when she might not have recorded the event in real time. This electronic diary was the only source document for the four co-primary endpoints. The diary was available to the subject throughout the day or night. To minimize recall, subjects were encouraged to enter hot flush data as soon as they experienced a hot flush, or at least once daily. Subjects were also provided with definitions of mild, moderate, and severe hot flushes, which conformed to those specified in the VMS Guidance.

3.2.2 Eligibility Criteria

Table 4 Inclusion Criteria for Studies 58, 59, and 64

Inclusion Criteria	
1	Postmenopausal women 18 to 70 years old who had experienced 7 or more moderate to severe hot flushes per day (or ≥50 per week) accompanied by sweating during the previous 30 days or longer.
2	Subject had amenorrhea for at least 12 months; amenorrhea for 6 – 12 months with serum FSH levels >40 mIU/L; or were ≥6 weeks post-surgical bilateral oophorectomy with or without hysterectomy.
3	Subject was willing to undergo minimum washout periods as follows: vaginal hormonal product (rings, gels, creams) ≥1 week; topical progesterone cream ≥1 week; transdermal estrogen or estrogen/progestin combination ≥4 weeks; oral estrogen or estrogen/progestin combination ≥8 weeks; intrauterine progestin therapy ≥8 weeks; progestin implants ≥3 months; estrogen injectable drug therapy ≥3 months; 81-0064 only: black cohosh, primrose oil, and other homeopathic remedies ≥1 week.
4	Subject must be able to enter simple commands and complete questionnaires on the frequency and severity score of their hot flushes using an electronic diary.
5	Subject had a daily average of at least 7 moderate to severe hot flushes and have completed at least 4 days (6 days for 81-0064) of diary entries during the baseline week(s) to be randomized to treatment.
6	Subjects treated with any antidepressant therapy (including the herbal supplement St. John's Wort) should have had no changes in their drug dosages during the previous month.
7	Subjects must have been able to function independently in all activities of daily life and be capable of reliable documentation.
8	Subjects must have signed the informed consent form.

FDA Comments:

- **Inclusion criteria were the strictest for Study 64. These women had to have moderate to severe hot flushes with a frequency of at least 7/day or 50/week for two consecutive weeks immediately before randomization, compared to one week in the other two studies.**
- **The inclusion criteria did not limit inclusion of women based on BMI, which is appropriate.**

Table 5 Exclusion Criteria for Studies 058, 59, and 64

Exclusion Criteria	
1	Subjects treated with gonadotropin releasing hormone agonists (e.g. leuprolide, goserelin); anti-estrogens (e.g. tamoxifen, toremifene, fulvestrant); or aromatase inhibitors (e.g. anastrozole, letrozole, exemestane) within 2 months prior to study start.
2	Subjects treated with estrogen pellets therapy within 6 months prior to study start (81-0058 and 81-0059 only).
3	Subjects treated with progestin injectable drug therapy within 6 months prior to study start (81-0058 and 81-0059 only).
4	Subjects who experienced only nighttime hot flushes or worked regular night shifts.
5	Subjects currently treated with gabapentin for other indications (including for vasomotor symptoms in 81-0064) were excluded. If a subject was using gabapentin for treatment of hot flushes, she could be screened after a 7-day washout if her hot flushes return (81-0058 and 81-0059 only).
6	Subjects who previously experienced dose-limiting adverse effects that prevented titration of gabapentin to an effective dosage.
7	Subjects with hypersensitivity to gabapentin (or pregabalin, 81-0064 only).
8	Subjects who were immunocompromised.

9	Subjects who had malignancy within the past 2 years other than basal cell carcinoma.
10	Subjects who had undergone gastric reduction surgery.
11	Subjects with severe chronic diarrhea, chronic constipation, uncontrolled irritable bowel syndrome (IBS), uncontrolled inflammatory bowel disease (IBD), or unexplained weight loss.
12	Subjects with any abnormal chemistry or hematology results that were deemed by the investigator to be clinically significant.
13	Subjects with an estimated/calculated GFR < 60 mL/min using the Cockcroft-Gault equation or the Modification of Diet in Renal Disease (MDRD) calculator.
14	Subjects who had a history of substance abuse within the past year.
15	Subjects currently taking morphine (81-0058 and 81-0059 only).
16	Subjects currently taking morphine or other opiates on a chronic basis (81-0064 only).
17	Subjects with a history of chronic hepatitis B or C, hepatitis within the past 3 months, or HIV infection.
18	Subjects who had any other serious medical condition that, in the opinion of the Investigator would jeopardize the safety of the subject or affect the validity of the study results.
19	Continuing use of any concomitant medication excluded by Inclusion Criterion 3.
20	Subjects who had participated in a clinical trial of an investigational drug or device within 30 days of the screening visit.
21	Subjects with suicidal ideation at initial completion of the Columbia-Suicide Severity Rating Scale (C-SSRS).(81-0064 only)

Source: CSR for Study 58, Section 9.3; Study 59, Section 9.3; Study 64, Section 9.3.

FDA Comment

It is noteworthy that the exclusion criteria excluded women with malignancy within the past two years. This may have excluded a significant portion of the potential target population for a nonhormonal VMS therapy.

3.3 Efficacy Assessments

3.3.1 Analysis Populations

The primary statistical analyses were conducted on the Intent to Treat (ITT) population (efficacy) and Safety population (safety), which were pre-defined by the Applicant as

- ITT population (this was the primary efficacy population): all randomized subjects who received at least one dose of study drug and had at least one post-randomization efficacy measure observed.
- Safety population: all randomized subjects who received at least one dose of their randomized treatment

The distribution of subjects in the various populations in the three phase 3 studies is displayed in Table 6.

Table 6 Summary of Analysis Populations, Phase 3 Studies

Analysis Population	Gabapentin (Daily Dose)		Placebo	Total
	1200 mg/day	1800 mg/day		
Study 58				
All randomized subjects	178	182	181	541
ITT population	174 (97.8%)	181 (99.5%)	177 (97.8%)	532 (98.3%)
Week 24 Completers	105 (59.0%)	119 (65.4%)	129 (71.3%)	353 (65.2%)
Study 59				
All randomized subjects	192	190	183	565
ITT population	186 (96.9%)	190 (100.0%)	183 (100.0%)	559 (98.9%)
Study 64				
All randomized subjects	N/A	302	298	600
ITT population	N/A	299 (99.0%)	294 (98.7%)	593 (98.8%)
Week 24 Completers	N/A	185 (61.3%)	177 (59.4%)	362 (60.3%)

ITT: intent-to-treat; N/A: not applicable
Week 24 Completers: subjects who completed 24 weeks of dosing in Studies 58 and 64.
Source: CSRs for Study 58,Table 14.1.3; Study 59, Table 14.1.3; Study 64, Table 14.1.3.

FDA Comments

- **The Applicant's ITT population was a modified ITT population, which was acceptable for the primary efficacy population.**
- **The number of subjects in the ITT population was very similar to the planned number to be enrolled.**

3.3.2 Efficacy Endpoints and Analyses

Primary Endpoint

In all three studies, the co-primary efficacy variables were:

- Mean change from baseline in average daily frequency of moderate to severe VMS at Week 4
- Mean change from baseline in average daily frequency of moderate to severe VMS at Week 12
- Mean change from baseline in average daily severity scores of moderate to severe VMS at Week 4
- Mean change from baseline in average daily severity scores of moderate to severe VMS at Week 12

The average daily frequency was defined as the average number of moderate or severe hot flushes self-reported daily during each treatment week, and the average daily severity score was defined as the average score of all moderate or severe hot flushes self-reported daily over reported days during each treatment week.

The severity (scoring) of hot flushes was defined as:

- Mild (1): sensation of heat without sweating
- Moderate (2): sensation of heat with sweating, able to continue activity
- Severe (3): sensation of heat with sweating, causing cessation of activity

A last observation carried forward (LOCF) approach was used for imputing missing data for average daily frequency and severity of moderate to severe hot flushes. If a subject had any missing diary days during a given week, the average daily frequency or severity score was calculated using available days without imputing the missing days.

Primary Analysis

Although two of the studies included two doses of gabapentin, the Applicant is seeking approval only for the 1800 mg dose, so the efficacy analyses described here are restricted to comparisons between the gabapentin 1800 mg arm and the placebo arm. The difference in treatment was compared at a two-sided alpha of 0.025 in Studies 58 and 59, and at a two-sided alpha of 0.05 in Study 64. The Applicant's protocol-specified statistical analysis methods were an ANCOVA model in Studies 58 and 59, and the non-parametric van Elteren test in Study 64 based on the ITT population. The ANCOVA model included baseline value as a covariate and fixed effects of treatment and center. The van Elteren (stratified Wilcoxon) test was stratified by study center.

As per protocol, efficacy needed to be demonstrated with respect to all four co-primary endpoints described above.

Secondary Endpoints

The Applicant pre-specified three subgroup analyses of women dichotomized on the basis of age
(< 65 vs. ≥ 65 years), race (Caucasian vs. non-Caucasian) and BMI (< 30 kg/m^2 vs. ≥ 30 kg/m^2).

Supportive Analyses

Clinical Meaningfulness of the Change in VMS frequency

As lower estrogen dose hormonal products for VMS and nonhormonal treatments have been evaluated, the FDA has observed that the magnitude of the treatment effect on VMS frequency is often less than that observed for "standard" dose hormonal therapies. In order to ensure that such treatment effects are still of clinical benefit to women, the FDA has requested that an analysis of the "clinical meaningfulness" of the change in VMS frequency be conducted for those products that do not demonstrate a placebo-adjusted reduction in VMS frequency from baseline of at least two moderate to severe hot flushes per day.

Because the placebo-adjusted reduction in VMS frequency in Studies 58 and 59 was observed to be less than two hot flushes/day, the Applicant pre-specified an analysis to evaluate the clinically meaningfulness of the change in VMS frequency in Study 64, using a discriminant analysis:

a). Three logistic regression models were applied, with the dependent variable being the Patient Global Impression Change (PGIC) category (improved vs. not improved) and the regressor variable being the Week 12 LOCF change (for the first model), Week 12 observed change (for the second model), and Week 24

observed change (for the third model) from baseline in frequency of moderate to severe hot flushes. In these models, all subjects were included, regardless of treatment group, and "improved" was considered the successful outcome.

b). The regressor value resulting in a fitted value of 0 (i.e., logit of 0.5) served as the cutoff value.

c). Subjects whose reduction from baseline in VMS frequency was better than the cutoff value (i.e., a greater reduction) were classified as responders, while those with VMS reductions less than or equal to the cutoff value were classified as non-responders.

d). Comparisons on responder rates between the gabapentin 1800 mg and placebo treatment groups were performed using Fisher's exact test at the two-sided, 0.05 level, separately for Week 12 and Week 24.

FDA Comment

The Applicant's discriminant analysis was considered a supportive analysis to support the primary efficacy findings. The study was not powered to conduct a statistical evaluation of the responder rate. In addition, the responder analysis was not controlled for type 1 error.

Persistence of Benefit in VMS Frequency

Persistence of benefit was assessed in Studies 58 and 64 by evaluating the change from baseline in VMS frequency at Week 24 and statistically comparing the treatment effects between gabapentin and placebo arms.

FDA Comment

FDA had agreed on the Week 24 endpoints as secondary efficacy endpoints. Tests on secondary endpoints were not controlled for type 1error.

Post Hoc Subgroup Analyses

The FDA also assessed efficacy in subjects dichotomized by age at menopause (< 45 vs. ≥ 45 years) as a surrogate for menopausal status (surgical vs. natural), which could not be derived from the dataset. Subgroup effects were evaluated by investigating the treatment-by-subgroup interaction at a two-sided alpha level of 0.05 in an ANCOVA model. If there was no statistically significant treatment-by-subgroup interaction effect, no further subgroup analyses were conducted.

4. Efficacy Results

4.1 Enrollment and Disposition

A total of 2,919 subjects were evaluated. Of these, 1,213 resulted in screen failures. The most common reason for screen failure was insufficient number of hot flushes. A total of 1,706 subjects were randomized in the phase 3 studies; 370 were randomized to receive gabapentin 1200 mg/day, 674 to receive 1800 mg/day, and 662 to receive placebo.

A total of 1,684 subjects were included in the ITT population (532, 559, and 593 in Studies 58, 59, and 64, respectively). A total of 715 subjects were included in the Week 24 primary efficacy population (353 in Study 58 and 362 in Study 64).

Subject disposition in the three phase 3 studies is shown in Table 7. In the integrated dataset, approximately 70% of subjects completed study medication across all treatment groups. Most subjects who withdrew from treatment in the gabapentin 1800 mg

treatment group did so due to adverse events (AEs, 13.3%) or withdrew consent (4.9%). A similar pattern was observed for the gabapentin 1200 mg treatment group, where 12.2% withdrew due to AEs and 5.3% withdrew consent. In the placebo treatment group, the most common reasons for withdrawal were lack of efficacy (7.8%) and withdrawn consent (7.5%).

Table 7 Disposition of Subjects: Studies 58, 59 and 64

	Study 58			Study 59			Study 64	
Reason for Discontinuation, n (%)	**Gabapentin (Daily Dose)**		**Placebo**	**Gabapentin (Daily Dose)**		**Placebo**	**Gabapentin 1800 mg/day**	**Placebo**
	1200 mg/day	**1800 mg/day**		**1200 mg/day**	**1800 mg/day**			
	N=178	**N=182**	**N=181**	**N=192**	**N=190**	**N=183**	**N=302**	**N=298**
Any discontinuation	60 (33.7)	49 (26.9)	37 (20.4)	32 (16.7)	38 (20.0)	36 (19.7)	94 (31.1)	104 (34.9)
Adverse event	28 (15.7)	20 (11.0)	7 (3.9)	15 (7.8)	21 (11.1)	8 (4.4)	48 (15.9)	35 (11.7)
Lack of efficacy	8 (4.5)	4 (2.2)	9 (5.0)	1 (0.5)	0	14 (7.7)	12 (4.0)	15 (5.0)
Protocol violation	2 (1.1)	1 (0.5)	1 (0.6)	2 (1.0)	1 (0.5)	1 (0.5)	7 (2.3)	13 (4.4)
Lost to follow-up	3 (1.7)	0	1 (0.6)	2 (1.0)	3 (1.6)	3 (1.6)	10 (3.3)	6 (2.0)
Death	0	0	0	0	1 (0.5)	0	0	1 (0.3)
Withdrawal of consent	12 (6.7)	12 (6.6)	12 (6.6)	7 (3.6)	7 (3.7)	8 (4.4)	13 (4.3)	28 (9.4)
Other reason	5 (2.8)	10 (5.5)	5 (2.8)	4 (2.1)	4 (2.1)	2 (1.1)	5 (1.7)	6 (2.0)
Missing	2 (1.1)	2 (1.1)	2 (1.1)	1 (0.5)	1 (0.5)	0	0	0

Source: CSRs for Study 58, Table 14.1.4; Study 59, Table 14.1.4; Study 64, Table 14.1.4

FDA Comments

- **Trends in discontinuations varied somewhat across studies. In Study 58, the two gabapentin arms had higher rates of overall discontinuations than the placebo arm, while this trend was reversed in the other two studies.**
- **Discontinuations due to AEs were higher in gabapentin arms than placebo in all three studies; however, there was no clear dose-response trend across the two gabapentin doses.**
- **A higher proportion of subjects in Study 64 discontinued early because of protocol violations (3.4% of the overall Safety Population) than reported in the other studies (≤0.8% of subjects). A higher proportion of subjects Lost to Follow-up was noted in Study 64 also.**

4.2 Demographic and Baseline Characteristics

Subjects had a mean age of approximately 53.4 years, were mostly white (67%), and had a mean BMI of 29 kg/m^2 in the pooled population of the three trials. The demographic characteristics were similar across all individual studies. Therefore, data from the integrated dataset are presented in Table 8.

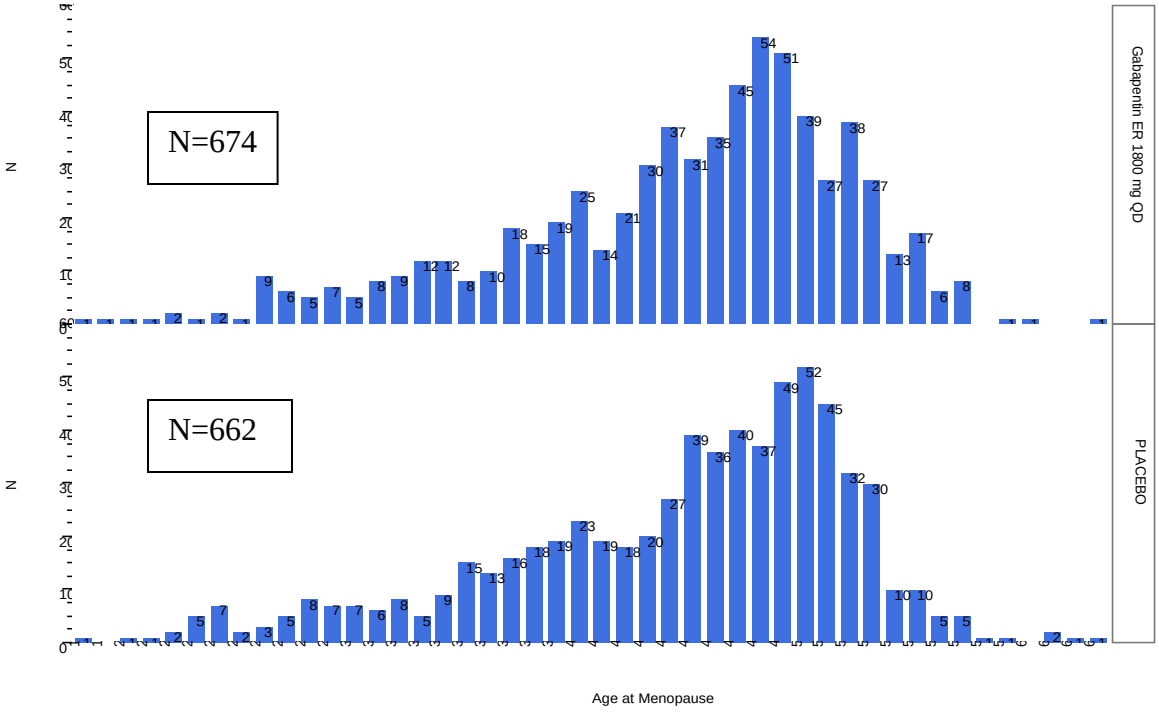
Table 8 Demographics and Baseline Characteristics (ITT Population, Pooled Phase 3 Data)

	Gabapentin 1800 mg (n=670)	Gabapentin 1200 mg (n=360)	Placebo (n=653)	Total (n=1683)
Age (years)				
Mean (SD)	53.6 (6.2)	53.0 (6.2)	53.4 (6.2)	53.4 (6.2)
Median	53	53	53	53
Min, max	24, 70	32, 70	25, 70	24, 70
Age, n (%)				
< 45	36 (5.4)	27 (7.5)	38 (5.8)	101 (6%)
≥ 45 to < 65	609 (90.8)	322 (89.4)	598 (91.6)	1613 (90.8)
≥ 65	33 (4.9)	15 (4.2)	25 (3.8)	73 (4.3)
Race, n (%)				
Caucasian	475 (70.9)	239 (66.4)	424 (64.9)	1138 (67.6)
Black	155 (23.1)	96 (26.7)	185 (28.3)	436 (25.9)
Asian	2 (0.3)	1 (0.3)	4 (0.6)	7 (0.4)
Hispanic	28 (4.2)	21 (5.8)	32 (4.9)	81 (4.8)
Other	10 (1.5)	3 (0.8)	9 (1.4)	22 (1.3)
BMI (kg/m^2), n (%)				
< 30	420 (62.7)	227 (63.1)	403 (61.7)	1050 (62.4)
≥ 30	249 (37.2)	133 (36.9)	251 (38.4)	633 (37.6)

BMI=Body mass index; SD=Standard
Source: Applicant's ISS, Table 10, p 32

The age at menopause was balanced across treatment groups in all three clinical trials, as shown in Figure 2. Almost half (41.5%) of the women experienced their menopause below age 45.

Figure 2 Age at Menopause by Treatment Arm, Pooled Phase 3 Data



Source: FDA Clinical Review

FDA Comment

The age of onset of menopause is below that in the general population (average age 52 years), and suggests that many of these subjects experienced some form of iatrogenic menopause, either due to oophorectomy, chemotherapy or premature ovarian failure.

4.3 Efficacy Findings

4.3.1 Statistical Issues in Efficacy Analysis

As per protocol, to support this indication, efficacy needed to be demonstrated with respect to all four co-primary endpoints. In addition, the Applicant agreed to conduct a secondary supportive analysis on the clinically meaningfulness of the reduction in VMS frequency in Study 64 if the placebo-corrected change from baseline in the daily hot flushes was < 2, and to demonstrate the persistence of benefit in VMS frequency at Week 24 in at least one study.

The Applicant's pre-specified ANCOVA analyses of Studies 58 and 59 are appropriate only if the data are normally distributed. When the data were analyzed, the Applicant concluded that the normality assumption was not met for either study; however, the Statistical Analysis Plans for the two studies failed to specify an alternative analysis to be done in such a situation.

After recognizing the skewed distribution of data in these two completed studies, the Applicant pre-specified a non-parametric analysis (which does not require normally distributed data) during the design of Study 64. At the FDA's request, the Applicant also conducted an ANCOVA analysis as a sensitivity analysis in this study.

The evaluations of clinical meaningfulness of the change in VMS frequency and of persistence of benefit in VMS frequency at Week 24 were to be conducted only if efficacy were demonstrated on the four co-primary efficacy endpoints.

4.3.2 Primary Efficacy Endpoint and Analysis

Results of the Applicant's analyses for Studies 58, 59 and 64 are summarized in Table 9. According to the Applicant's pre-specified analyses for each study, none of the studies met all four co-primary efficacy endpoints. Studies 58 and 59 were required to obtain a p-value < 0.025 to achieve statistical significance for each co-primary endpoint because two gabapentin doses were evaluated in each study.

Study 58 failed on the reduction in VMS frequency and severity at Week 12. Study 59 and Study 64 both failed on the reduction in VMS frequency at Week 12.

Across the three studies, the treatment differences in the reduction from baseline in VMS frequency at Week 4 were similar (-1.5 to -1.6 hot flushes per day). The effect waned in all three studies at Week 12, but particularly in Studies 58 and 64, in which the treatment difference dropped to -0.5 to -0.6 hot flushes/day. The treatment differences in the reduction from baseline in VMS severity varied considerably across studies, but were statistically significant in favor of gabapentin at both Weeks 4 and 12 in all three studies.

Table 9 Mean Changes in Daily Frequency and Severity of Moderate to Severe Hot Flushes at Weeks 4 and 12 (LOCF, ITT Population)

Study	Frequency			Severity		
	Gaba 1800 mg	Placebo	*Treatment Difference	Gaba 1800 mg	Placebo	*Treatment Difference
Study 58:						
N	181	177		181	177	
Baseline (Mean)	11.1	11.3		2.48	2.49	
Change from baseline						
Week 4						
LS Mean	-7.3	-6.0	-1.5	-0.61	-0.29	-0.32
p-value			**<0.001***			**<0.001***
Week 12						
LS Mean	-7.4	-6.9	-0.5	-0.74	-0.55	-0.20
p-value			0.20			0.047
Study 59:						
N	190	183		190	183	
Baseline (Mean)	11.2	11.2		2.51	2.46	
Change from baseline						
Week 4						
LS Mean	-6.9	-5.4	-1.5	-0.65	-0.37	-0.28
p-value			**0.004***			**<0.001***
Week 12						
LS Mean	-7.3	-6.2	-1.1	-0.83	-0.54	-0.29
p-value			0.028			**0.003***
Study 64:						
N	299	294		299	294	
Baseline (Mean)	11.8	12.0		2.55	2.54	
Change from baseline						
Week 4						
Median	-6.4	-4.9	-1.6	-0.18	-0.05	-0.13
p-value			**<0.001***			**<0.001***
Week 12						
Median	-7.1	-6.6	-0.6	-0.32	-0.14	-0.18
p-value			0.1			**<0.001***

Bold = p-values below the requisite level for statistical significance
LS = least squares
****Statistical significant at two-sided alpha of 0.025 for the first 2 studies and 0.05 for the last study**
Note: p-values for Studies 58 and 59 are based on LS means
Source: FDA Statistical Reviewer's Analysis

FDA sensitivity analyses evaluated the impact of missing data using both mixed model repeated measure (MMRM) analysis and ANCOVA model with LOCF. The missing data did not affect the efficacy conclusions based on either LOCF imputation or MMRM analysis. Treatment differences based on LOCF values were similar to those using observed values, indicating that the impact of missing data was similar in both treatment arms.

4.3.3 Clinical Meaningfulness of Change in VMS Frequency

Because Study 64 failed to meet the co-primary efficacy endpoint of frequency reduction at Week 12, the planned assessment of the clinical meaningfulness of the change in VMS frequency is not warranted.

4.3.4 Persistence of Benefit in VMS Frequency

Because Studies 58 and 64 failed to meet the co-primary efficacy endpoint of frequency reduction at Week 12, the planned assessments of the persistence of benefit in VMS frequency at Week 24 are not warranted.

4.3.5 Post Hoc Efficacy Subgroup Analyses Results

Subgroups based on age, race, BMI and age at menopause (as a surrogate for menopausal etiology) were evaluated by the FDA statistical reviewer; these are routine exploratory analyses. A treatment-by-subgroup interaction was noted only for race in Study 64, but due to the small number of non-Caucasian subjects no further analyses were conducted.

4.4 Overall Summary of Efficacy

Per the FDA analysis, data from the three phase 3 studies showed that:

1. Study 58 demonstrated a statistically significant reduction in VMS frequency at Week 4 but not at Week 12. Therefore, no further evaluation of whether the change in VMS frequency persisted at Week 24 was warranted.
2. Study 59 demonstrated a statistically significant reduction in VMS frequency at Week 4 but not at Week 12 when adjusted for multiple dose comparisons. The Applicant did not specify an evaluation either of clinical meaningfulness or of persistence of benefit in this study.
3. Study 64 demonstrated a statistically significant reduction in VMS frequency at Week 4 but not at Week 12. Therefore, no further evaluation of whether the change in VMS frequency was clinically meaningful or whether the benefit in VMS frequency reduction persisted at Week 24 was warranted.
4. Study 58 demonstrated a statistically significant reduction in VMS severity at Week 4, but not at Week 12 when adjusted for multiple dose comparisons. Studies 59 and 64 demonstrated statistically significant reductions in VMS severity at Weeks 4 and 12.

5. Safety Finding from Gabapentin Clinical Trials

5.1 Overview of the Safety Database for Gabapentin

In addition to postmarketing safety information on the approved Gralise product, the gabapentin safety database includes data pooled from the three phase 3 studies; data from the other phase 1 and 2 studies had design differences that precluded pooling. The Applicant defined treatment-emergent AEs (TEAEs) as any AE occurring from randomization through three days after End of Treatment. A total of 1,686 subjects were treated in the gabapentin phase 3 studies, of which 671 subjects received gabapentin 1800 mg, 360 received gabapentin 1200 mg and 655 received placebo. Of these, 270 subjects in the gabapentin 1800 mg group and 280 in the placebo group completed 24 weeks of treatment. The safety analysis set was defined as all randomized subjects in phase 3

studies who took at least one dose of study drug. The number of subjects and duration of exposure for the safety database is shown in Table 10.

Table 10 Drug Exposure by Duration, Pooled Phase 3 Data

Category	Gabapentin 1800 mg N=671 n (%)	Gabapentin 1200 mg N=360 n (%)	Placebo N=655 n (%)
≥ 1 day to < 4 weeks	64 (9.5)	33 (9.2)	53 (8.1)
≥ 4 weeks to < 12 weeks	66 (9.8)	34 (9.4)	78 (11.9)
≥ 12 weeks to < 24 weeks	256 (38.2)	175 (48.6)	233 (35.6)
≥ 24 weeks	270 (40.2)	113 (31.4)	280 (42.7)

Source: Modified from Applicant's ISS, Table 1.5, p 23

FDA Comments

- **At the Pre-NDA Meeting of April 10, 2012, the FDA stated that pooling the safety data from the three phase 3 trials was acceptable.**
- **Safety data from the phase 2 study (Study 56) was not integrated into the dataset due to differences in the doses studied and duration of treatment.**

5.2 Deaths

Two subjects died during the phase 3 program, one on gabapentin 1800 mg in Study 59 and one on placebo in Study 64. The placebo subject died of a hemorrhagic stroke. The gabapentin subject narrative is described here briefly:

- A 49-year-old female randomized to the gabapentin 1800 mg treatment group in Study 59 died due to accidental fentanyl overdose on Study Day 43. The subject had a history of overactive bladder, cervical spine fusion, pins, rods and plates in her right foot, and insomnia. Concomitant medication included trazodone. About a month after her first dose of gabapentin, the subject was found by her family deceased at home reportedly with one fentanyl patch on her body (more recent information indicates she was wearing four patches). The subject's last visit was one week before her death, and it was determined that her last dose of study drug was the day prior to her death. In the autopsy report, a detailed toxicology screen showed detectable levels of methadone and hydrocodone in addition to fentanyl, bupropion, and citalopram. In addition, it was noted that the subject had a history of schizophrenia and bipolar disorder (not disclosed to the study), and that the attending physician indicated that the fentanyl patches had not been prescribed to the subject.

FDA Comment

The possibility of suicide cannot be ruled out based on the information provided.

5.3 Non-fatal Serious Adverse Events

Serious adverse events (SAEs) were reported in 12 gabapentin 1800 mg subjects (1.8%), four subjects (1.1%) in the gabapentin 1200 mg group and 13 subjects (2.0%) in the placebo group in the pooled safety database. Including all treatment arms, the highest rate of SAEs (2.3%) was observed in Study 58, with overall rates of 1.1% and 1.8% in Studies 59 and 64, respectively.

The most common SAEs reported in the gabapentin group were malignancies (five subjects) and overdoses (two subjects). SAEs that occurred in any treatment arm are listed in Table 11. Malignancies are discussed further in Section 5.5.

Table 11 SAEs, Phase 3 Studies

	Treatment	Age Race	Adverse Event	AE Start Week	Action taken
Study 58					
1	Gaba 1200	45 Caucasian	Breast cancer	21	Dose not changed
2	Gaba 1800	50 Caucasian	Urinary tract infection	20	Dose not changed
3	Gaba 1800	54 Caucasian	Nerve compression	19	Drug interrupted
4	Gaba 1800	50 Caucasian	Lung neoplasm malignant	15	Drug withdrawn
5	Gaba 1800	48 Caucasian	Rib fracture	24	Dose not changed
6	Gaba 1800	57 Caucasian	Pneumothorax	4	Dose not changed
7	Gaba 1200	52 Caucasian	Gastroesophageal reflux disease	11	Dose not changed
10	Gaba 1800	58 Hispanic	Breast cancer	8	Drug withdrawn
8	Placebo	40 Caucasian	Abdominal hernia	22	Drug interrupted
9	Placebo	42 Caucasian	Cerebrovascular disorder	20	Dose not changed
11	Placebo	55 Black	Chest pain	25	Dose not changed
12	Placebo	63 Caucasian	Coronary artery disease	3	Drug interrupted
Study 59					
1	Gaba 1200	48 Caucasian	Overdose and Suicide attempt	9	Drug withdrawn
2	Gaba 1800	45 Black	Chest pain	13	Dose not changed
3	Gaba 1200	63 Caucasian	Ovarian cancer	6	Drug withdrawn
4	Gaba 1800	49 Caucasian	Accidental overdose	7	Drug withdrawn (subject died)
5	Placebo	36 Caucasian	Road traffic accident	8	Drug withdrawn
6	Placebo	47 Black	Meniscus lesion	10	Dose not changed
Study 64					
1	Gaba 1800	57 Caucasian	Anemia	24	Drug interrupted
2	Gaba 1800	70 Caucasian	Arthritis infective	26	Dose not changed
3	Gaba 1800	55 Hispanic	Periorbital cellulitis	4	Drug withdrawn

	Treatment	Age Race	Adverse Event	AE Start Week	Action taken
4	Gaba 1800	59 Caucasian	Chronic lymphocytic leukemia	5	Drug withdrawn
5	Placebo	55 Black	Acute sinusitis, asthma and musculoskeletal chest pain	2	Drug interrupted
6	Placebo	53 Caucasian	Palpitations	24	Dose not changed
7	Placebo	54 Caucasian	Hemorrhagic stroke	11	Drug withdrawn (subject died)
8	Placebo	43 Black	Pneumonia primary atypical	4	Dose not changed
9	Placebo	60 Black	Acute myocardial infarction	5	Drug withdrawn
10	Placebo	48 Black	Bronchitis acute	11	Dose not changed
11	Placebo	50 Caucasian	Hypertension	12	Dose not changed

Source: Clinical reviewer's analysis of Applicant's ADAE dataset from ISS datasets

FDA Comments

- **In addition to the death due to fentanyl overdose, an additional subject on gabapentin 1200 mg in Study 59 was hospitalized as an apparent attempted suicide after being found unresponsive on Study Day 53. She had a medical history that included depression and was concomitantly taking medications including Lyrica (pregabalin) and Cymbalta. She had taken an overdose of multiple drugs including benzodiazepines, a tricyclic antidepressant, Seroquel and Percocet. She was discharged to an inpatient behavioral health facility, and the site indicated that she was not discontinued due to the SAE of attempted suicide.**
- **Two of the malignancies occurred in the gabapentin 1200 mg arm, and three in the gabapentin 1800 mg arm; none occurred among placebo subjects. However, three cases were diagnosed in the first two months of treatment. The remaining cases, one case each of breast cancer and lung cancer occurred in Treatment Month 5 and 3, respectively. The short duration of gabapentin exposure in these subjects makes an association with study drug unlikely and suggests that these cancers were likely pre-existing. Baseline mammograms were not done in these studies.**

5.4 Discontinuations due to Adverse Events

A total of 92 subjects (13.7%) in the gabapentin 1800 mg group, 44 subjects (12.2%) in the gabapentin 1200 mg group and 49 subjects (7.5%) in the placebo group had AEs leading to study drug discontinuation. Most AEs causing discontinuation were within the Nervous System Disorder System Organ Class (SOC). Dizziness was the most commonly occurring AE that led to discontinuation in the gabapentin treatment groups, occurring in 2.7% of the gabapentin 1800 mg group and 2.8% of the gabapentin 1200 mg group, compared to 0.3% of the placebo group. Somnolence led to discontinuation in 1.9% of subjects in each of the gabapentin treatment groups and in 0.6% of subjects in the placebo treatment group. AEs that resulted in discontinuation in two or more subjects and more frequently in gabapentin compared to placebo arms are reported in Table 12.

Table 12 Adverse Events Leading to Study Drug Discontinuation, Pooled Phase 3 Data

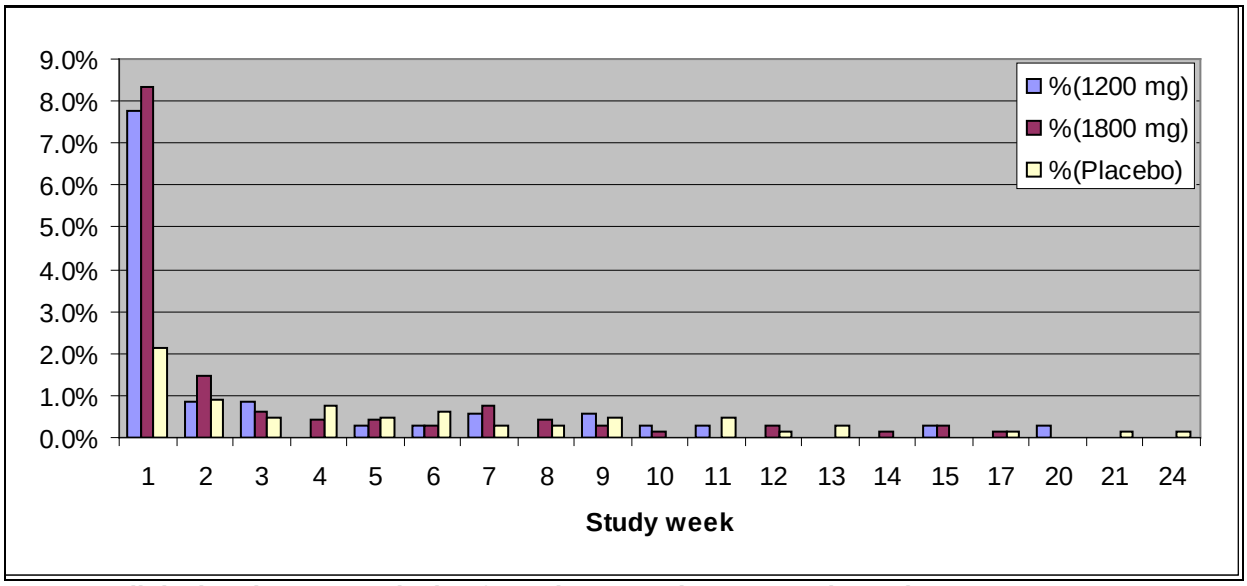
AE	Gabapentin 1800 mg N=671		Gabapentin 1200 mg N=360		Placebo N=655	
	N	%	N	%	N	%
Dizziness	18	2.7	10	2.8	2	0.3
Somnolence	13	1.9	7	1.9	4	0.6
Headache	6	0.9	0	0	3	0.5
Nausea	6	0.9	0	0	1	0.2
Sedation	3	0.4	2	0.6	0	0
Lethargy	3	0.4	1	0.3	0	0
Disorientation	3	0.4	1	0.3	0	0
Myalgia	3	0.4	0	0	0	0
Vertigo	3	0.4	2	0.6	0	0

Source: Clinical reviewer's analysis using JMP (Applicant's ADAE dataset-ISS)

FDA Comment
Although AEs leading to discontinuation occurred more frequently in the gabapentin arms, there is no clear dose-response demonstrated.

The majority of discontinuations occurred within the first week (titration week). During Week 1, more subjects in the gabapentin 1800 mg group (56, 8.3%) than in the placebo group (14, 2.1%) reported AEs leading to discontinuation. Figure 3 shows the timing of AE discontinuations by treatment arm. In all three trials, subjects had their dose titrated during the first week of therapy, although the titration regimen differed slightly in Study 64.

Figure 3 Timing of AEs Leading to Discontinuation by Treatment Group, Pooled Phase 3 Data



Source: Clinical reviewer's analysis of ISS dataset using JMP and Excel programs

FDA Comment
The slightly different dose titration regimen in Study 64 did not have marked impact on the rate of early discontinuations due to AEs. It is not clear that the optimal titration regimen has been determined.

5.5 Other Adverse Events of Interest

The Applicant pre-specified suicide-related events as being of specific interest; FDA requires evaluation of suicidality for centrally-acting drugs, such as selective serotonin reuptake inhibitors (SSRIs). FDA also requested the Applicant to evaluate taper-emergent AEs that might represent withdrawal effects.

The FDA clinical reviewer evaluated a variety of Standardized MedDRA Queries (SMQs) in the pooled safety dataset. There were no safety signals that warranted further exploration identified in this evaluation.

Suicidality

Suicidal ideation was assessed per protocol in Study 64. The Columbia Suicide Severity Rating Scale (C-SSRS) questionnaire was used to classify each subject as to whether she experienced a possible tendency for suicide in this study at screening, at Weeks 4, 12, and 24 and at a follow-up visit at Week 28 (four weeks after the end of the treatment period) or, for dropouts, four weeks after early termination. Incidence rates for suicidal ideation were then compared between the gabapentin and placebo-treatment groups.

A search for "yes" responses to questions regarding suicidal ideation or behavior at any visit beyond the screening visit yielded 14 responses by eight subjects. These findings are summarized in Table 13 below.

Table 13 Subjects with Positive Responses to Items on the C-SSRS During Treatment or Follow-up

TX Grp	Visit	Items Endorsed (see the key below)
Gabapentin	Week 28	SI-1, SI-2, SI-3, SI-4.
Placebo	Week 24/ET	SI-1, SI-4, SB5.
Placebo	Week 24/ET	SI-1.
Gabapentin	Week 12	SI-1.
Gabapentin	Week 28	SB-6
Gabapentin	Week 4	SI-1
Gabapentin	Week 24/ET	SI-1.
Gabapentin	Week 12	SI-2, SI-3.

C-SSRS Item Key:
SI-1 = wish to be dead.
SI-2= non-specific active suicidal thoughts.
SI-3 = active suicidal thoughts by any method, no specific plan or intent.
SI-4 = active suicidal thoughts with some intent to act but no specific plan.
SB5 = preparatory acts or behavior.
SB6 = suicidal behavior present during the rating period.

Overall, there were 2.0% (6/300) of gabapentin subjects and 0.7% (2/295) of placebo subjects who reported suicidal ideation or behavior on the C-SSRS during the treatment period or the follow-up period.

FDA Comments

- **Although this represents a three-fold increased risk of suicidal adverse events for drug versus placebo, this difference is not statistically significant (p= 0.3, 2-tailed Fishers exact test) owing to the small number of events.**
- **The Division of Psychiatry Products was consulted to evaluate the suicidality data. While the reviewer did not agree with all the Applicant's conclusions, he recommended that standard class labeling with regard to suicidality be included in the label, and that additional labeling was not warranted.**

A prospective evaluation of emergent suicidal ideation or behavior was not conducted in Studies 56, 58, or 59. Therefore, the examination of AEs related to suicidal thoughts or behavior in Studies 56, 58, and 59 is not adequate to assess suicidality because a) proactive questioning may be necessary to detect such events, b) suicidal events may not always be recognized as such, especially by investigators outside the mental health field; and c) the description of suicidal events can use highly variable terminology and result in some events being missed. Thus, no conclusions can be drawn regarding the emergence of suicidal ideation or behavior in these three trials. Currently, the prescribing information for gabapentin includes standard class labeling for suicidality in the Warnings and Precautions section.

Malignancy

All five SAEs related to cancer occurred in one of the gabapentin arms. Brief narratives are provided in Table 14.

Table 14 Malignancy Narratives

Treatment	Serious Adverse Event	Details
Gabapentin 1800 mg	Lung neoplasm malignant	50 year old Caucasian woman received the first dose of gabapentin and was hospitalized for lung cancer 3.5 months later. **The Applicant reports that no further information can be obtained** for this event. Study drug was discontinued 10 days before the hospitalization.
Gabapentin 1800 mg	Breast cancer	58 year old Hispanic woman received the first dose of gabapentin two months before being diagnosed with breast cancer in the right breast. A core biopsy of the right breast in the 10 o'clock position was obtained. The pathology report revealed invasive ductal carcinoma, Black's Modified Nuclear Grade 1. It was also noted that the 2.5 cm mass in the right axillary tail had been palpable for nine months and increasing in size. **The Applicant reported that no further information can be obtained.** Dosing was not changed.
Gabapentin 1200 mg	Breast cancer	A 46 year old Caucasian female received the first dose of gabapentin five months before she was diagnosed with right breast cancer after a mammogram. A breast core biopsy was interpreted as an invasive ductal carcinoma with medullary features grade III. Breast prognostic factor studies revealed ER and PR - negative; HER-2/neu - negative; CK5/6 - positive; proliferation index - 80%. Six weeks after diagnosis, the subject underwent right modified radical mastectomy, sentinel lymph node biopsy, left total mastectomy and breast reconstruction. Final path showed: greatest dimension 2.3 cm, no regional lymph node metastasis. The subject completed the study a week before her surgery, with last dose of study drug taken 10 days prior to surgery.
Gabapentin 1200 mg	Ovarian cancer	63 year old Caucasian woman received first dose of gabapentin two weeks before she underwent a CT of the abdomen and pelvis which revealed fluid within the pelvis with omental caking and a mass-like appearance of both the left and right ovaries, mass-like densities in the pelvis posteriorly, one lying between the uterus and the rectum measuring 2.5 x 5.0 cm, a subcentimeter cystic lesion in the liver, and a small diaphragmatic node on the right and degenerative changes of the spine. Three weeks after the CT, the subject reported ovarian cancer stage 3 and study drug was discontinued.
Gabapentin 1800 mg	Chronic lymphocytic leukemia	59 year old Caucasian female took gabapentin for about one month before she reported a diagnosis of chronic lymphocytic leukemia. She discontinued study drug before this diagnosis was classified as an SAE. Five months before starting gabapentin, initial screening labs showed a white blood count (WBC) of 12.91 (units and reference range not provided) and lymphocytes of 9.31. Two weeks before starting study drug, her labs showed a WBC of 15.06 (units and reference range not provided) and lymphocytes of 10.2 (units and reference range not provided). The subject was referred to her primary care physician who thought this was due to a possible virus as the subject had sinus issues.

Source: Clinical reviewer's summary of subject narratives from phase 3 trials

In addition, six gabapentin and two placebo subjects had AEs reported in the Neoplasms SOC. Because these were not coded as SAEs, narratives were not provided; however, it appears that aside from one case (an intraductal papilloma of the breast in a gabapentin 1800 mg subject), these were benign lesions.

FDA Comment
There is insufficient information about Cases 1 and 3 to make a determination as to whether they might be drug-related. The remaining cases appear to have been diagnosed too soon after initiation of study drug to make an association likely.

Age-AE Interactions

Dizziness was the most common AE reported by the 73 subjects in the ≥ 65 year old subpopulation and occurred at a higher frequency in the older subjects than in those < 65 years of age. In the gabapentin 1800 mg treatment group, 24.2% of older subjects ≥ 65 years reported this AE compared with 15.8% of younger subjects; in the gabapentin 1200 mg treatment group, 33.3% of older subjects reported dizziness compared to 19.7% of younger subjects. In the placebo arm, no subjects < 65 years reported dizziness; 3.2% of those 65 years or older reported dizziness.

5.6 Common Adverse Events

The most common AEs in the pooled phase 3 dataset with higher incidence in the gabapentin arm are reported in Table 15. Dizziness, somnolence, and balance disorders were the most common AEs occurring more frequently in the drug group than placebo.

Table 15 Common Adverse Events with Higher Incidence in Gabapentin Arm, Pooled Phase 3 Data

	Gabapentin 1800 mg N = 671		Placebo N = 655		Gabapentin 1800 mg vs. Placebo
Preferred Term	**n**	**%**	**n**	**%**	**RD (per 100)**
Dizziness	109	16.2	20	3.1	13.2
Somnolence	69	10.3	18	2.8	7.5
Disorientation	17	2.5	0	0.0	2.5
Nausea	40	6.0	20	3.1	2.9
Sedation	9	1.3	1	0.2	1.2
Amnesia	5	0.8	0	0.0	0.8
Vertigo	9	1.3	2	0.3	1.0
Balance disorder	7	1.0	1	0.2	0.9
Gastroesophageal reflux disease	7	1.0	1	0.2	0.9
Vomiting	18	2.7	8	1.2	1.5
Dry mouth	20	3.0	10	1.5	1.5
Fall	6	0.9	1	0.2	0.7
Musculoskeletal stiffness	4	0.6	0	0.0	0.6
Edema peripheral	9	1.3	3	0.5	0.9
Disturbance in attention	7	1.0	2	0.3	0.7
Contusion	8	1.2	3	0.5	0.7

RD= risk difference.
Source: Clinical reviewer's analysis of AE and DM datasets using MAED program.

As seen above, drowsiness, somnolence, and sedation are terms that could be used interchangeably (when an AE is coded in the datasets). In assessing these AEs, it is informative to group similar terms together. Looking at the higher level terms (HLT) of the coding hierarchy allows consideration of related terms together. Table 16 shows the tabulation of AEs in which similar events are combined (at the HLT level). This table gives a better assessment of the absolute risk difference between the two groups. For example, more subjects experienced AEs related to neurological signs and symptoms and disturbance in consciousness in the gabapentin 1800 group compared to the placebo group.

Table 16 Common Adverse Events (Top 10 HLTs, Phase 3 Studies)

	Gabapentin 1800 mg N = 671		Placebo N = 655		Gabapentin 1800 mg vs. Placebo
Higher Level Term	**n**	**%**	**n**	**%**	**RD (per 100)**
Neurological signs and symptoms NEC	109	16.2	20	3.1	13.1
Disturbances in consciousness NEC	84	12.5	21	3.2	9.3
Nausea and vomiting symptoms	51	7.6	26	4.0	3.6
Oral dryness and saliva altered	20	3.0	10	1.5	1.5
Confusion and disorientation	18	2.7	0	0.0	2.7
Mental impairment (excluding dementia and memory loss)	12	1.8	2	0.3	1.5
Inner ear signs and symptoms	10	1.5	3	0.5	1.0
Memory loss (excluding dementia)	10	1.5	3	0.5	1.0
Non-site specific injuries NEC	10	1.5	3	0.5	1.0
Cerebellar coordination and balance disturbances	8	1.2	1	0.2	1.0

NEC = Not Elsewhere Classified RD = risk difference
Source: Clinical reviewer's analysis of AE and DM datasets using MAED program. Only HLTs occurring more frequently in the drug group are included in the table.

FDA Comment
Given the centrally acting mechanism of gabapentin, the observation of markedly greater rates of central nervous system AEs is biologically plausible.

Subjects experienced higher number of AEs while coming off gabapentin 1800 mg compared to placebo. Study 64 included a visit at Week 28 (4 weeks after completing the treatment phase of the study at Week 24 and discontinuing study medication). Of the 600 subjects randomized in this study, 397 (66%) completed 24 weeks therapy and 393 of these subjects returned for the Week 28 visit. The adverse events reported by more than one subject between Weeks 24 and 28 are shown in Table 17. More subjects in the gabapentin 1800 mg group (11.7%) reported AEs following discontinuation of study drug compared to placebo (7.8%).

Table 17 Discontinuation-Emergent AEs w/ Higher Incidence in Gabapentin Arm, Study 64

Preferred Term	Gabapentin 1800 mg N = 300 n (%)	Placebo N = 295 n (%)
Any AE	35 (11.7)	23 (7.8)
Hepatic enzyme increase	2 (0.7)	0
Hypercalcemia	2 (0.7)	0
Headache	2 (0.7)	1 (0.3)
Migraine	2 (0.7)	0
Anxiety	2 (0.7)	0
Depression	2 (0.7)	0
Hot flush	2 (0.7)	0

Source: Applicant's response to information request, dated November 1, 2012, p 8

Although there was no formal follow-up visit following treatment discontinuation in Studies 58 and 59, the following adverse events were reported by more than one subject in any treatment group (see Table 18). Again, the incidence of AE's following discontinuation of study drug was higher in the gabapentin 1800 mg arm (13.2%), compared to placebo (6.1%). The incidence in the gabapentin 1200 mg arm was 7.2%.

Table 18 Discontinuation-Emergent AEs with Higher Incidence in Gabapentin Arm, Studies 58 and 59

Preferred Term	Gabapentin 1800 mg N = 371 n (%)	Gabapentin 1200 mg N = 360 n (%)	Placebo N = 360 n (%)
Any AE	49 (13.2)	26 (7.2)	22 (6.1)
Nausea	3 (0.8)	4 (1.1)	0
Insomnia	3 (0.8)	0	1 (0.3)
Vertigo	2 (0.5)	1 (0.3)	0
Weight increased	2 (0.5)	1 (0.3)	0
Dizziness	2 (0.5)	2 (0.6)	0
Somnolence	2 (0.5)	0	0
Vomiting	0	2 (0.6)	0
Liver function test abnormal	0	2 (0.6)	1 (0.3)

Source: Applicant's response to information request, dated November 1, 2012, p 9

FDA Comment
Overall, discontinuation-emergent AEs occurred more frequently in the drug group compared to the placebo group. However, no distinct syndrome could be identified and no dose-response relationship can be determined.

5.7 Vital Signs

There were no notable changes from baseline in blood pressure, pulse or respiratory rate in any treatment arm.

5.8 Laboratory Findings

Assessment of hematological parameters over time showed no major clinical differences between the gabapentin and placebo groups.

Clinical chemistries included albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, blood urea nitrogen, calcium, chloride, creatinine kinase, creatinine, creatinine clearance, cholesterol, triglycerides, lactate dehydrogenase, potassium, sodium, total protein, and uric acid. Shift tables for chemistry parameters for the gabapentin group showed no clinically meaningful changes over time.

5.9 Postmarketing Safety Reports

From the time of the market launch through April 2012, it is estimated that more than 20,000 patients have been exposed to Gralise. The most commonly-reported spontaneous AEs included dizziness, fatigue, insomnia, somnolence, and nausea. No new safety signals have been identified post-marketing with Gralise.

5.10 Summary of Safety

Table 19 Summary of AEs, Pooled Phase 3 Studies

Category	Gabapentin 1800 mg N=671 n (%)	Gabapentin 1200 mg N=360 n (%)	Placebo N=655 n (%)
Subjects with any TEAE	449 (66.9)	235 (65.3)	348 (53.1)
Deaths	1 (0.1)	0	1 (0.2)
Subjects with SAEs	12 (1.8)	4 (1.1)	13 (2.0)
Subjects with study drug discontinuations due to a TEAE	92 (13.7)	44 (12.2)	49 (7.5)
Subjects with a malignancy SAE	3 (0.4)	2 (0.6)	0
Subjects with suicidality (Study 64 only*)	6 (2.0)	NA	2(0.7)
Subjects with discontinuation-emergent AE			
Study 58 and 59	49 (13.2)	26 (7.2)	22 (6.1)
Study 64	35 (11.7)	NA	23 (7.8)

***Denominators in Study 64 are 300 for gabapentin 1800 mg and 295 for placebo**
NA = not assessed
Source: Clinical reviewer's analysis

Overall, the incidence of TEAEs generally, discontinuation-emergent AEs and discontinuations due to AEs was higher in the gabapentin 1800 mg than the placebo treatment arm. No clear dose-response was evident when considering the gabapentin 1200 mg dose as well. Deaths and SAEs were equally distributed across treatment arms. The incidence of malignancies categorized as SAEs and of suicidality-related events, while low, was numerically greater in the gabapentin 1800 mg arm. However, the timing of the cancers in these fairly short-term studies makes a relationship to study drug less likely. Currently labeling addresses the risk of suicidality.

Appendices

1. **Approved Labeling for Gralise**

2. **Draft Guidance for Industry, Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation, January 2003**

3. **Schedule of Events, Phase 3 Studies**

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GRALISE safely and effectively. See full prescribing information for GRALISE.

GRALISE® (gabapentin) tablets
Initial U.S. Approval: 1993

INDICATIONS AND USAGE

GRALISE is indicated for the management of Postherpetic Neuralgia (PHN).
Important Limitation: GRALISE is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration *(See Warnings and Precautions)*

DOSAGE AND ADMINISTRATION

- GRALISE should be titrated to an 1800 mg dose taken orally, once-daily, with the evening meal. GRALISE tablets should be swallowed whole. Do not crush, split, or chew the tablets. (2.1)
- If GRALISE dose is reduced, discontinued, or substituted with an alternative medication, this should be done gradually over a minimum of 1 week or longer (at the discretion of the prescriber). (2.1)
- Renal impairment: Dose should be adjusted in patients with reduced renal function. GRALISE should not be used in patients with CrCl less than 30 or in patients on hemodialysis. (2.2)

DOSAGE FORMS AND STRENGTHS

- 300 and 600 mg tablets (3)

CONTRAINDICATIONS

GRALISE is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients. (4)

WARNINGS AND PRECAUTIONS

- GRALISE is not interchangeable with other gabapentin products
- Antiepileptic drugs, including gabapentin, the active ingredient in GRALISE, increase the risk of suicidal thoughts or behavior (5.1)
- Increased seizure frequency may occur in patients with seizure disorders if GRALISE is rapidly discontinued. Withdraw GRALISE gradually over a minimum of 1 week. (5.2)

ADVERSE REACTIONS

- The most common adverse reaction (greater than or equal to 5% and twice placebo) is dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Depomed, Inc. at 1-866-458-6389 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- An increase in gabapentin AUC values have been reported when administered with hydrocodone. (7.6)
- An increase in gabapentin AUC values have been reported when administered with morphine. (7.7)
- An antacid containing aluminum hydroxide and magnesium hydroxide reduced the bioavailability of gabapentin immediate release by about approximately 20%, but by only 5% when gabapentin was taken 2 hours after antacids. It is recommended that GRALISE be taken at least 2 hours following antacid administration. (7.10)

USE IN SPECIFIC POPULATIONS

- Pregnancy: GRALISE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- Nursing Mothers: GRALISE should be used in women who are nursing only if the benefits clearly outweigh the risks. (8.3)
- Elderly: Reductions in GRALISE dose should be made in patients with age-related compromised renal function. (8.5)
- Renal impairment: Dosage adjustment is necessary for patients with impaired renal function. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Revised: 08/2012

FULL PRESCRIBING INFORMATION: CONTENTS *

*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GRALISE is indicated for the management of postherpetic neuralgia.

GRALISE is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.

2 DOSAGE AND ADMINISTRATION

2.1 Postherpetic Neuralgia

Do not use GRALISE interchangeably with other gabapentin products.

Titrate GRALISE to an 1800 mg dose taken orally once daily with the evening meal. GRALISE tablets should be swallowed whole. Do not split, crush, or chew the tablets.

If GRALISE dose is reduced, discontinued, or substituted with an alternative medication, this should be done gradually over a minimum of one week or longer (at the discretion of the prescriber).

In adults with postherpetic neuralgia, GRALISE therapy should be initiated and titrated as follows:

Table 1: GRALISE Recommended Titration Schedule

	Day 1	Day 2	Days 3-6	Days 7-10	Days 11-14	Day 15
Daily Dose	300 mg	600 mg	900 mg	1200 mg	1500 mg	1800 mg

2.2 Patients with Renal Impairment

In patients with stable renal function, creatinine clearance (C_{Cr}) can be reasonably well estimated using the equation of Cockcroft and Gault:

For females $C_{Cr}=(0.85)(140\text{-age})(\text{weight})/[(72)(S_{Cr})]$

For males $C_{Cr}=(140\text{-age})(\text{weight})/[(72)(S_{Cr})]$

where age is in years, weight is in kilograms and S_{Cr} is serum creatinine in mg/dL.

The dose of GRALISE should be adjusted in patients with reduced renal function, according to Table 2. Patients with reduced renal function must initiate GRALISE at a daily dose of 300 mg. GRALISE should be titrated following the schedule outlined in Table 1. Daily dosing in patients with reduced renal function must be individualized based on tolerability and desired clinical benefit.

Table 2: GRALISE Dosage Based on Renal Function

Once-daily dosing	
Creatinine Clearance (mL/min)	GRALISE Dose (once daily with evening meal)
≥ 60	1800 mg
30 - 60	600 mg to 1800 mg
< 30	GRALISE should not be administered
patients receiving hemodialysis	GRALISE should not be administered

3 DOSAGE FORMS AND STRENGTHS

Tablets: 300 mg and 600 mg *[see Description (11) and How Supplied/Storage and Handling (16)]*

4 CONTRAINDICATIONS

GRALISE is contraindicated in patients with demonstrated hypersensitivity to the drug or its ingredients.

5 WARNINGS AND PRECAUTIONS

GRALISE is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.

The safety and effectiveness of GRALISE in patients with epilepsy has not been studied.

5.1 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including gabapentin, the active ingredient in GRALISE, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 3 shows absolute and relative risk by indication for all evaluated AEDs.

Table 3: Risk by Indication for Antiepileptic Drugs (including gabapentin, the active ingredient in GRALISE) in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing GRALISE must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which products containing active components that are AEDs (such as gabapentin, the active component in GRALISE) are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that GRALISE contains gabapentin which is also used to treat epilepsy and that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or

worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.2 Withdrawal of Gabapentin

Gabapentin should be withdrawn gradually. If GRALISE is discontinued, this should be done gradually over a minimum of 1 week or longer (at the discretion of the prescriber).

5.3 Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats. The clinical significance of this finding is unknown.

In clinical trials of gabapentin therapy in epilepsy comprising 2,085 patient-years of exposure in patients over 12 years of age, new tumors were reported in 10 patients, and pre-existing tumors worsened in 11 patients, during or within 2 years after discontinuing the drug. However, no similar patient population untreated with gabapentin was available to provide background tumor incidence and recurrence information for comparison. Therefore, the effect of gabapentin therapy on the incidence of new tumors in humans or on the worsening or recurrence of previously diagnosed tumors is unknown.

5.4 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan Hypersensitivity, has been reported in patients taking antiepileptic drugs, including GRALISE. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. GRALISE should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

5.5 Laboratory Tests

Clinical trial data do not indicate that routine monitoring of clinical laboratory procedures is necessary for the safe use of GRALISE. The value of monitoring gabapentin blood concentrations has not been established.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 359 patients with neuropathic pain associated with postherpetic neuralgia have received GRALISE at doses up to 1800 mg daily during placebo-controlled clinical studies. In clinical trials in patients with postherpetic neuralgia, 9.7% of the 359 patients treated with GRALISE and 6.9% of 364 patients treated with placebo discontinued prematurely due to adverse reactions. In the GRALISE treatment group, the most common reason for discontinuation due to adverse reactions was dizziness. Of GRALISE-treated patients who experienced adverse reactions in clinical studies, the majority of those adverse reactions were either "mild" or "moderate".

Table 4 lists all adverse reactions, regardless of causality, occurring in at least 1% of patients with neuropathic pain associated with postherpetic neuralgia in the GRALISE group for which the incidence was greater than in the placebo group.

Table 4: Treatment-Emergent Adverse Reaction Incidence in Controlled Trials in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at Least 1% of all GRALISE-Treated Patients and More Frequent Than in the Placebo Group)

Body System - Preferred Term	GRALISE N = 359 %	Placebo N = 364 %
Ear and Labyrinth Disorders		
Vertigo	1.4	0.5
Gastrointestinal Disorders		
Diarrhea	3.3	2.7
Dry mouth	2.8	1.4
Constipation	1.4	0.3
Dyspepsia	1.4	0.8
General Disorders		
Peripheral edema	3.9	0.3
Pain	1.1	0.5

Infections and Infestations		
Nasopharyngitis	2.5	2.2
Urinary tract infection	1.7	0.5
Investigations		
Weight increased	1.9	0.5
Musculoskeletal and Connective Tissue Disorders		
Pain in extremity	1.9	0.5
Back pain	1.7	1.1
Nervous System Disorders		
Dizziness	10.9	2.2
Somnolence	4.5	2.7
Headache	4.2	4.1
Lethargy	1.1	0.3

In addition to the adverse reactions reported in Table 4 above, the following adverse reactions with an uncertain relationship to GRALISE were reported during the clinical development for the treatment of postherpetic neuralgia. Events in more than 1% of patients but equally or more frequently in the GRALISE-treated patients than in the placebo group included blood pressure increase, confusional state, gastroenteritis viral, herpes zoster, hypertension, joint swelling, memory impairment, nausea, pneumonia, pyrexia, rash, seasonal allergy, and upper respiratory infection.

6.2 Postmarketing and Other Experience with other Formulations of Gabapentin

In addition to the adverse experiences reported during clinical testing of gabapentin, the following adverse experiences have been reported in patients receiving other formulations of marketed gabapentin. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: angioedema, blood glucose fluctuation, breast enlargement, elevated creatine kinase, elevated liver function tests, erythema multiforme, fever, hyponatremia, jaundice, movement disorder, Stevens-Johnson syndrome.

Adverse events following the abrupt discontinuation of gabapentin immediate release have also been reported. The most frequently reported events were anxiety, insomnia, nausea, pain and sweating.

7 DRUG INTERACTIONS

In vitro studies were conducted to investigate the potential of gabapentin to inhibit the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) that mediate drug and xenobiotic metabolism using isoform selective marker substrates and human liver microsomal preparations. Only at the highest concentration tested (171 mcg/mL; 1 mM) was a slight degree of inhibition (14% to 30%) of isoform CYP2A6 observed. No inhibition of any of the other isoforms tested was observed at gabapentin concentrations up to 171 mcg/mL (approximately 15 times the C_{max} at 3600 mg/day).

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs. The drug interaction data described in this section were obtained from studies involving healthy adults and adult patients with epilepsy.

7.1 Phenytoin

In a single (400 mg) and multiple dose (400 mg three times daily) study of gabapentin immediate release in epileptic patients (N=8) maintained on phenytoin monotherapy for at least 2 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin and phenytoin had no effect on gabapentin pharmacokinetics.

7.2 Carbamazepine

Steady-state trough plasma carbamazepine and carbamazepine 10, 11 epoxide concentrations were not affected by concomitant gabapentin immediate release (400 mg three times daily; N=12) administration. Likewise, gabapentin pharmacokinetics were unaltered by carbamazepine administration.

7.3 Valproic Acid

The mean steady-state trough serum valproic acid concentrations prior to and during concomitant gabapentin immediate release administration (400 mg three times daily; N=17) were not different and neither were gabapentin pharmacokinetic parameters affected by valproic acid.

7.4 Phenobarbital

Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin immediate release (300 mg three times daily; N=12) are identical whether the drugs are administered alone or together.

7.5 Naproxen
Coadministration of single doses of naproxen (250 mg) and gabapentin immediate release (125 mg) to 18 volunteers increased gabapentin absorption by 12% to 15%. Gabapentin immediate release had no effect on naproxen pharmacokinetics. The doses are lower than the therapeutic doses for both drugs. The effect of coadministration of these drugs at therapeutic doses is not known.

7.6 Hydrocodone
Coadministration of gabapentin immediate release (125 mg and 500 mg) and hydrocodone (10 mg) reduced hydrocodone C_{max} by 3% and 21%, respectively, and AUC by 4% and 22%, respectively. The mechanism of this interaction is unknown. Gabapentin AUC values were increased by 14%; the magnitude of the interaction at other doses is not known.

7.7 Morphine
When a single dose (60 mg) of controlled-release morphine capsule was administered 2 hours prior to a single dose (600 mg) of gabapentin immediate release in 12 volunteers, mean gabapentin AUC values increased by 44% compared to gabapentin immediate release administered without morphine. The pharmacokinetics of morphine were not affected by administration of gabapentin immediate release 2 hours after morphine. The magnitude of this interaction at other doses is not known.

7.8 Cimetidine
Cimetidine 300 mg decreased the apparent oral clearance of gabapentin by 14% and creatinine clearance by 10%. The effect of gabapentin immediate release on cimetidine was not evaluated. This decrease is not expected to be clinically significant.

7.9 Oral Contraceptives
Gabapentin immediate release (400 mg three times daily) had no effect on the pharmacokinetics of norethindrone (2.5 mg) or ethinyl estradiol (50 mcg) administered as a single tablet, except that the C_{max} of norethindrone was increased by 13%. This interaction is not considered to be clinically significant.

7.10 Antacid (containing aluminum hydroxide and magnesium hydroxide)
An antacid containing aluminum hydroxide and magnesium hydroxide reduced the bioavailability of gabapentin immediate release by about approximately 20%, but by only 5% when gabapentin immediate release was taken 2 hours after the antacid. It is recommended that GRALISE be taken at least 2 hours following the antacid (containing aluminum hydroxide and magnesium hydroxide) administration.

7.11 Probenecid
Gabapentin immediate release pharmacokinetic parameters were comparable with and without probenecid, indicating that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid.

7.12 Drug/Laboratory Test Interactions
False positive readings were reported with the Ames-N-Multistix SG® dipstick test for urine protein when gabapentin was added to other antiepileptic drugs; therefore, the more specific sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 3 to 8 times the maximum dose of 1800 mg/day given to PHN patients on a mg/m^2 basis. The no effect level was 500 mg/kg/day representing approximately the maximum recommended human dose [MRHD] on a mg/m^2 body surface area (BSA) basis. When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to approximately 3 to 11 times the MRHD on a mg/m^2 BSA basis. There was an increased incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are approximately 3 to 11 times the maximum human dose of 1800 mg/day on a mg/m^2 basis; the no-effect doses were approximately 5 times (Fertility and General Reproductive Performance study) and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m^2 BSA basis. Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared to controls in offspring of mice, rats, or rabbits given doses up to 100 times (mice), 60 times (rats), and 50 times (rabbits) the human daily dose on a mg/kg basis, or 8 times (mice), 10 times (rats), or 16 times (rabbits) the human daily dose on a mg/m^2 BSA basis. In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300, and 1500 mg/kg/day, or 0.6 to 16 times the maximum human

dose on a mg/m^2 BSA basis. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
To provide information regarding the effects of *in utero* exposure to GRALISE, physicians are advised to recommend that pregnant patients taking GRALISE enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

8.3 Nursing Mothers
Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, GRALISE should be used in women who are nursing only if the benefits clearly outweigh the risks.

8.4 Pediatric Use
The safety and effectiveness of GRALISE in the management of postherpetic neuralgia in patients less than 18 years of age has not been studied.

8.5 Geriatric Use
The total number of patients treated with GRALISE in controlled clinical trials in patients with postherpetic neuralgia was 359, of which 63% were 65 years of age or older. The types and incidence of adverse events were similar across age groups except for peripheral edema, which tended to increase in incidence with age.
GRALISE is known to be substantially excreted by the kidney. Reductions in GRALISE dose should be made in patients with age-related compromised renal function. *[see Dosage and Administration (2.2)]*.

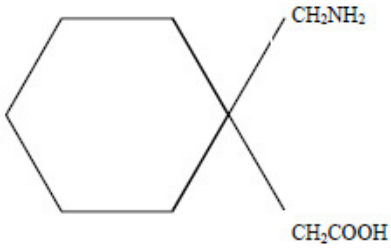
8.6 Hepatic Impairment
Because gabapentin is not metabolized, studies have not been conducted in patients with hepatic impairment.

8.7 Renal Impairment
GRALISE is known to be substantially excreted by the kidney. Dosage adjustment is necessary in patients with impaired renal function. GRALISE should not be administered in patients with CrCL between 15 and 30 or in patients undergoing hemodialysis. *[see Dosage and Administration (2.2)]*.

9 DRUG ABUSE AND DEPENDENCE
The abuse and dependence potential of GRALISE has not been evaluated in human studies.

10 OVERDOSAGE
A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation.
Acute oral overdoses of gabapentin immediate release in humans up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea were observed. All patients recovered with supportive care.
Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

11 DESCRIPTION
Gabapentin is 1-(aminomethyl)cyclohexaneacetic acid; γ-amino-2-cyclohexyl-butyric acid with a molecular formula of $C_9H_{17}NO_2$ and a molecular weight of 171.24.
The structural formula is:



Gabapentin is a white to off-white crystalline solid with a pKa1 of 3.7 and a pKa2 of 10.7. It is freely soluble in water and acidic and basic solutions. The log of the partition coefficient (n-octanol/ 0.05 M phosphate buffer) at pH 7.4 is -1.25.
GRALISE is supplied as tablets containing 300 mg or 600 mg of gabapentin. GRALISE tablets swell in gastric fluid and gradually release gabapentin. Each 300 mg tablet contains the inactive ingredients copovidone, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene oxide, and Opadry® II white. Opadry® II white contains polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol 3350, and lecithin (soya). Each 600 mg tablet contains the inactive ingredients copovidone, hypromellose,

magnesium stearate, polyethylene oxide, and Opadry® II beige. Opadry® II beige contains polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol 3350, iron oxide yellow, and iron oxide red.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action by which gabapentin exerts its analgesic action is unknown but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). Gabapentin prevents pain-related responses in several models of neuropathic pain in rats and mice (e.g., spinal nerve ligation models, spinal cord injury model, acute herpes zoster infection model). Gabapentin also decreases pain-related responses after peripheral inflammation (carrageenan footpad test, late phase of formulin test), but does not alter immediate pain-related behaviors (rat tail flick test, formalin footpad acute phase). The relevance of these models to human pain is not known.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid), but it does not modify $GABA_A$ or $GABA_B$ radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. In radioligand binding assays at concentrations up to 100 μM, gabapentin did not exhibit affinity for a number of other receptor sites, including benzodiazepine, glutamate, N-methyl-D-aspartate (NMDA), quisqualate, kainate, strychnine-insensitive or strychnine-sensitive glycine; alpha 1, alpha 2, or beta adrenergic; adenosine A1 or A2; cholinergic, muscarinic, or nicotinic; dopamine D1 or D2; histamine H1; serotonin S1 or S2; opiate mu, delta, or kappa; cannabinoid 1; voltage-sensitive calcium channel sites labeled with nitrendipine or diltiazem; or at voltage-sensitive sodium channel sites labeled with batrachotoxinin A20-alpha-benzoate. Gabapentin did not alter the cellular uptake of dopamine, noradrenaline, or serotonin.

In vitro studies with radiolabeled gabapentin have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus. A high-affinity binding protein in animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium channels. However, functional correlates of gabapentin binding, if any, remain to be elucidated. It is hypothesized that gabapentin antagonizes thrombospondin binding to α2δ-1 as a receptor involved in excitatory synapse formation and suggested that gabapentin may function therapeutically by blocking new synapse formation.

12.2 Pharmacodynamics

No pharmacodynamic studies have been conducted with GRALISE.

12.3 Pharmacokinetics

Absorption and Bioavailability

Gabapentin is absorbed from the proximal small bowel by a saturable L-amino transport system. Gabapentin bioavailability is not dose proportional; as the dose is increased, bioavailability decreases.

When GRALISE (1800 mg once daily) and gabapentin immediate release (600 mg three times a day) were administered with high fat meals (50% of calories from fat), GRALISE has a higher C_{max} and lower AUC at steady state compared to gabapentin immediate release (Table 5). Time to reach maximum plasma concentration (T_{max}) for GRALISE is 8 hours, which is about 4-6 hours longer compared to gabapentin immediate release.

Table 5: Mean (SD) Steady-State Pharmacokinetics for GRALISE and Gabapentin Immediate Release in Plasma of Healthy Subjects (Day 5, n = 21)

Pharmacokinetic Parameters (Mean ± SD)	**GRALISE 1800 mg QD**	**Gabapentin Immediate Release 600 mg TID**
AUC_{0-24} (ng•hr/mL)	132,808 ± 34,701	141,301 ± 29,759
C_{max} (ng/mL)	9,585 ± 2,326	8,536 ± 1,715
C_{min} (ng/mL)	1,842 ± 654	2,588 ± 783
T_{max} (hr) median (range)	8 (3-12)	2 (1-5)*

* = relative to most recent dose

Do not use GRALISE interchangeably with other gabapentin products because of differing pharmacokinetic profiles that affect frequency of administration.

GRALISE should be taken with evening meals. If it is taken on an empty stomach, the bioavailability will be substantially lower. Administration of GRALISE with food increases the rate and extent of absorption of gabapentin compared to the fasted state. C_{max} of gabapentin increases 33-84% and AUC of gabapentin increases 33-118% with food depending on the fat content of the meal. GRALISE should be taken with food.

Distribution

Gabapentin is less than 3% bound to plasma proteins. After 150 mg intravenous administration, the mean ± SD volume of distribution is 58 ± 6 L.

Metabolism and Excretion

Gabapentin is eliminated by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans. In patients with normal renal function given gabapentin immediate release 1200 to 3000 mg/day, the drug elimination half-life ($t_{1/2}$) was 5 to 7 hours. Elimination kinetics do not change with dose level or multiple doses.
Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance. In elderly patients and patients with impaired renal function, plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.
Dosage adjustment in patients with compromised renal function is necessary. In patients undergoing hemodialysis, GRALISE should not be administered *[see Dosage and Administration (2.2)]*.

12.4 Special Populations
Renal Insufficiency: As renal function decreases, renal and plasma clearances and the apparent elimination rate constant decrease, while C_{max} and $t_{1/2}$ increase.
In patients (N=60) with creatinine clearance of at least 60, 30 to 59, or less than 30 mL/min, the median renal clearance rates for a 400 mg single dose of gabapentin immediate release were 79, 36, and 11 mL/min, respectively, and the median $t_{1/2}$ values were 9.2, 14, and 40 hours, respectively.
Dosage adjustment is necessary in patients with impaired renal function *[see Dosage and Administration (2.2)]*.
Hemodialysis: In a study in anuric adult subjects (N=11), the apparent elimination half-life of gabapentin on nondialysis days was about 132 hours; during dialysis the apparent half-life of gabapentin was reduced to 3.8 hours. Hemodialysis thus has a significant effect on gabapentin elimination in anuric subjects. GRALISE should not be administered in patients undergoing hemodialysis. Alternative formulations of gabapentin products should be considered in patients undergoing hemodialysis.
Elderly: Apparent oral and renal clearances of gabapentin decrease with increasing age, although this may be related to the decline in renal function with age. Reductions in gabapentin dose should be made in patients with age-related compromised renal function *[see Dosage and Administration (2.2)]*.
Hepatic Impairment: Because gabapentin is not metabolized, studies have not been conducted in patients with hepatic impairment.
Pediatrics: The pharmacokinetics of GRALISE have not been studied in patients less than 18 years of age.
Gender: Although no formal study has been conducted to compare the pharmacokinetics of gabapentin in men and women, it appears that the pharmacokinetic parameters for males and females are similar and there are no significant gender differences.
Race: Pharmacokinetic differences due to race have not been studied. Because gabapentin is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenoma and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg/day were more than 10 times higher than plasma concentrations in humans receiving 1800 mg per day and in rats receiving 1000 mg/kg/day peak plasma concentrations were more than 6.5 times higher than in humans receiving 1800 mg/day. The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. The relevance of this finding to carcinogenic risk in humans is unclear.
Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro* and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans.
Gabapentin did not demonstrate mutagenic or genotoxic potential in 3 *in vitro* and 4 *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was negative in the *in vivo* mouse micronucleus assay; and it did not induce unscheduled DNA synthesis in hepatocytes from rats given gabapentin.
No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 11 times the maximum recommended human dose on an mg/m^2 basis).

14 CLINICAL STUDIES
The efficacy of GRALISE for the management of postherpetic neuralgia was established in a double-blind, placebo-controlled, multicenter study. This study enrolled patients between the age of 21 to 89 with postherpetic neuralgia persisting for at least 6 months following healing of herpes zoster rash and a minimum baseline pain intensity score of at least 4 on an 11-point numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain).
This 11-week study compared GRALISE 1800 mg once daily with placebo. A total of 221 and 231 patients were treated with GRALISE or placebo, respectively. The study treatment including titration for all patients comprised a 10-week treatment period

followed by 1-week of dose tapering. Double-blind treatment began with titration starting at 300 mg/day and titrated up to a total daily dose of 1800 mg over 2 weeks, followed by 8 weeks fixed dosing at 1800 mg once daily, and then 1 week of dose tapering. During the 8-week stable dosing period, patients took 3 active or placebo tablets each night with the evening meal. During baseline and treatment, patients recorded their pain in a daily diary using an 11-point numeric pain rating scale. The mean baseline pain score was 6.6 and 6.5 for GRALISE and placebo-treated patients, respectively.
Treatment with GRALISE statistically significantly improved the endpoint mean pain score from baseline. For various degrees of improvement in pain from baseline to study endpoint, Figure 1 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement.

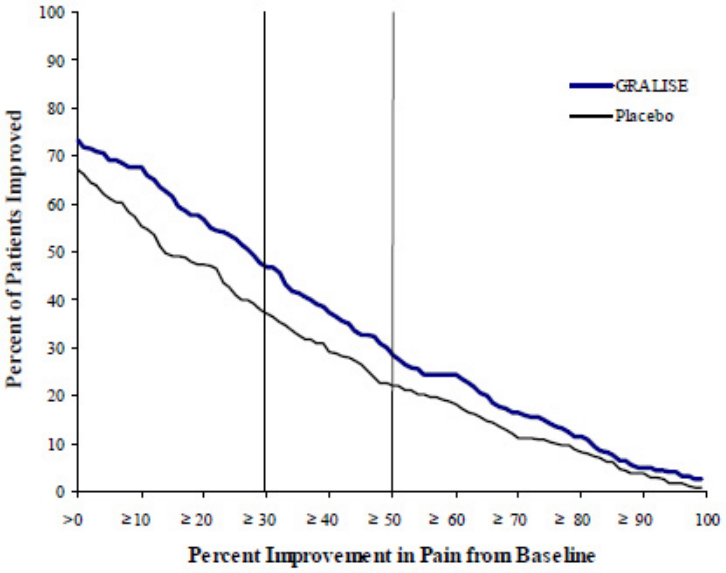


Figure 1: Percent of Patients Achieving Various Levels of Pain Relief

16 HOW SUPPLIED/STORAGE AND HANDLING
GRALISE (gabapentin) Tablets are supplied as follows:
300 mg tablets:
GRALISE 300 mg tablets are white, oval shaped tablets debossed with "SLV" on one side and "300" on the other side.
NDC 13913-004-13 (Bottle of 30)
600 mg tablets:
GRALISE 600 mg tablets are beige, oval shaped tablets debossed with "SLV" on one side and "600" on the other side.
NDC 13913-005-19 (Bottle of 90)
30-Day Starter Pack:
NDC 13913-006-16 (Blister package containing 78 tablets: 9 x 300 mg tablets and 69 x 600 mg tablets)
Storage
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].
Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION
- Advise patients that GRALISE is not interchangeable with other formulations of gabapentin.
- Advise patients to take GRALISE only as prescribed. GRALISE may cause dizziness, somnolence, and other signs and symptoms of CNS depression.
- Advise patients not to drive or operate other complex machinery until they have gained sufficient experience on GRALISE to gauge whether or not it adversely affects their mental and/or motor performance. Advise patients who require concomitant treatment with morphine to tell their prescriber if they develop signs of CNS depression such as somnolence. If this occurs the dose of GRALISE or morphine should be reduced accordingly.
- Advise patients that if they miss a dose of GRALISE to take it with food as soon as they remember. If it is almost time for the next dose, just skip the missed dose and take the next dose at the regular time. Do not take two doses at the same time.
- Advise patients that if they take too much GRALISE, to call their healthcare provider or poison control center, or go to the nearest emergency room right away.

17.1 Medication Guide
Advise patients of the availability of a Medication Guide, and instruct them to read the Medication Guide prior to taking GRALISE.

17.2 Suicidal Thoughts and Behavior
Advise patients, their caregivers, and families that AEDs, including gabapentin, the active ingredient in GRALISE, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers *[see Warnings and Precautions (5.1)]*.

17.3 Dosing and Administration
Advise patients that GRALISE should be taken orally once-daily with the evening meal. GRALISE tablets should be swallowed whole. Do not split, crush, or chew the tablets *[see Dosage and Administration (2.1)]*.

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Depomed, Inc.
Menlo Park, CA 94025

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MEDICATION GUIDE

GRALISE® (gra leez')
(gabapentin) Tablets
Read this Medication Guide before you start taking GRALISE and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. If you have any questions about GRALISE, ask your healthcare provider or pharmacist.

What is the most important information I should know about GRALISE?
Do not stop taking GRALISE without first talking with your healthcare provider. Stopping GRALISE suddenly can cause serious problems.
Like other antiepileptic drugs, gabapentin, the active ingredient in GRALISE, may cause suicidal thoughts or actions in a very small number of people, about 1 in 500. However, it is not known if GRALISE is safe and effective in people with seizure problems (epilepsy). Therefore, GRALISE should not be used in place of other gabapentin products.
Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

How can I watch for early symptoms of suicidal thoughts and actions?
- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

• Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Do not stop taking GRALISE without first talking with your healthcare provider.
• Stopping GRALISE suddenly can cause serious problems.

What is GRALISE?
GRALISE is a prescription medicine used in adults, 18 years and older, to treat:
• pain from damaged nerves (neuropathic pain) that follows healing of shingles (a painful rash that comes after a herpes zoster infection).

It is not known if GRALISE is safe and effective in people with seizure problems (epilepsy).
It is not known if GRALISE is safe and effective in children under 18 years of age with postherpetic pain.
GRALISE is not interchangeable with other gabapentin products.
Who should not take GRALISE?
Do not take GRALISE if you are allergic to gabapentin or any of the ingredients in GRALISE. See the end of this Medication Guide for a complete list of ingredients in GRALISE.
What should I tell my healthcare provider before taking GRALISE?
Before taking GRALISE, tell your healthcare provider if you:
• have or have had depression, mood problems or suicidal thoughts or behavior

• have seizures

• have kidney problems or get kidney dialysis

• are pregnant or plan to become pregnant. It is not known if GRALISE can harm your unborn baby. Tell your healthcare provider right away if you become pregnant while taking GRALISE. You and your healthcare provider will decide if you should take GRALISE while you are pregnant.
• If you become pregnant while taking GRALISE, talk to your healthcare provider about registering with the North American Antiepileptic Drug (NAAED) Pregnancy Registry. The purpose of this registry is to collect information about the safety of antiepileptic drugs, including gabapentin, the active ingredient in GRALISE, during pregnancy. You can enroll in this registry by calling 1-888-233-2334.

• are breastfeeding or plan to breastfeed. GRALISE can pass into your breast milk. You and your healthcare provider should decide how you will feed your baby while you take GRALISE.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins or herbal supplements.
Taking GRALISE with certain other medicines can cause side effects or affect how well they work. Do not start or stop other medicines without talking to your healthcare provider.
Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.
How should I take GRALISE?
• Take GRALISE exactly as prescribed. Your healthcare provider will tell you how much GRALISE to take and when to take it. Take GRALISE at the same time each day.

• **Do not change your dose or stop taking GRALISE without talking with your healthcare provider.** If you stop taking GRALISE suddenly, you may experience side effects. Talk with your healthcare provider about how to stop GRALISE slowly.

• Take GRALISE with food one time each day with your evening meal.

• Take GRALISE tablets whole. Do not split, crush, or chew GRALISE tablets before swallowing.

• Your healthcare provider may change your dose of GRALISE. Do not change your dose of GRALISE without talking to your healthcare provider.

• If you miss a dose, take it as soon as you remember with food. If it is almost time for your next dose, just skip the missed dose. Take the next dose at your regular time. **Do not take two doses at the same time.**

• If you take too much GRALISE, call your healthcare provider or poison control center, or go to the nearest emergency room right away.

- If you are taking an antacid containing aluminum hydroxide and magnesium hydroxide, it is recommended that GRALISE be taken at least 2 hours following administration of the antacid.

What should I avoid while taking GRALISE?
- Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking GRALISE without first talking to your healthcare provider. Taking GRALISE with alcohol or medicines that cause sleepiness or dizziness may make your sleepiness or dizziness worse.

- Do not operate heavy machines or do other dangerous activities until you know how GRALISE affects you. GRALISE can slow your thinking and motor skills.

What are the possible side effects of GRALISE?
The most common side effect of GRALISE is:
- dizziness

Tell your healthcare provider about any side effect that bothers you or that does not go away.
These are not all the possible side effects of GRALISE. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store GRALISE?
Store GRALISE at 59°F to 86°F (15°C to 30°C)
- **Keep GRALISE and all medicines out of the reach of children.**

General information about the safe and effective use of GRALISE
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use GRALISE for a condition for which it was not prescribed. Do not give GRALISE to other people, even if they have the same symptoms you have. It may harm them.
This Medication Guide summarizes the most important information about GRALISE. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about GRALISE that is written for health professionals.
For more information about GRALISE, call 1-866-458-6389.

What are the ingredients in GRALISE?
Active ingredient: gabapentin
Inactive ingredients:
300 mg tablet: copovidone, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene oxide, and Opadry® II white. Opadry® II white contains polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol 3350, and lecithin (soya).
600 mg tablet: copovidone, hypromellose, magnesium stearate, polyethylene oxide, and Opadry® II beige. Opadry® II beige contains polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol 3350, iron oxide yellow, and iron oxide red.

Marketed by:
Depomed, Inc.
Menlo Park, CA 94025
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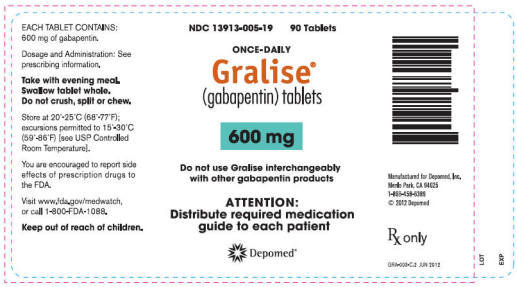
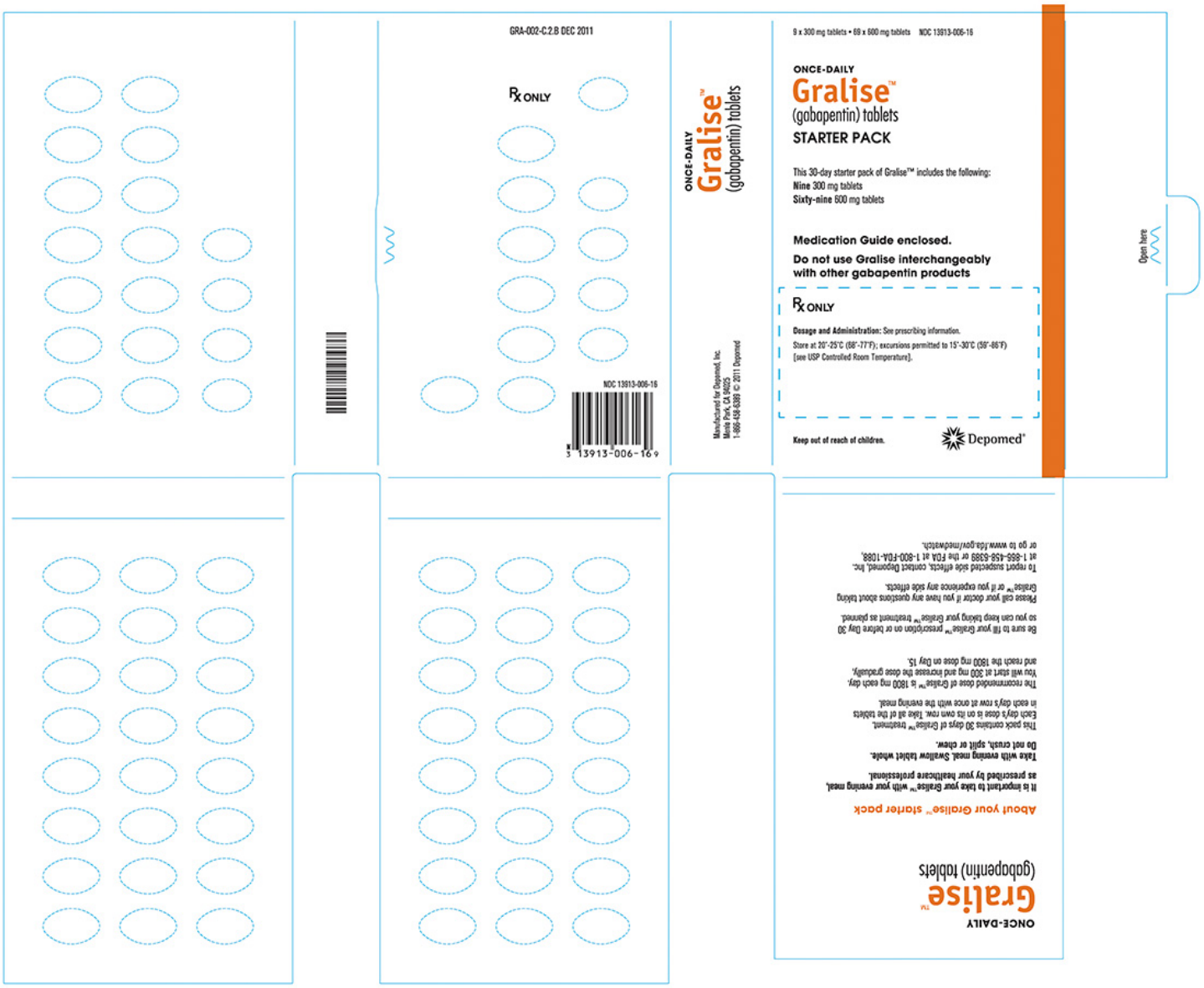
GRA-004-C.3 AUG 2012
Issued AUG 2012
This Medication Guide has been approved by the U.S. Food and Drug Administration.

PRINCIPAL DISPLAY PANEL - 300 mg Tablets
NDC 13913-004-13
30 Tablets
ONCE-DAILY
Gralise®
(gabapentin) tablets
300 mg
Do not use Gralise interchangeably with other gabapentin products
ATTENTION: Distribute required medication guide to each patient
Depomed®

PRINCIPAL DISPLAY PANEL - 600 mg Tablets
NDC 13913-005-19
90 Tablets
ONCE-DAILY
Gralise®
(gabapentin) tablets
600 mg
Do not use Gralise interchangeably with other gabapentin products
Distribute required medication guide to each patient
Depomed®



PRINCIPAL DISPLAY PANEL - 30-Day Starter Pack
NDC 13913-006-16
9 x 300 mg tablets • 69 x 600 mg tablets
ONCE-DAILY
Gralise®
(gabapentin) tablets
STARTER PACK
This 30-day starter pack of Gralise® includes the following:
Nine 300 mg tablets
Sixty-nine 600 mg tablets
Medication Guide enclosed.
Do not use Gralise interchangeably with other gabapentin products
R_x ONLY
Dosage and Administration: See prescribing information.
Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].
Keep out of reach of children.
Depomed®



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Guidance for Industry

Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on the content of the draft document contact Margaret Kober at 301-827-4243

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2003
Clinical/Medical

Guidance for Industry

Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation

Additional copies are available from:

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2003
Clinical/Medical

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Guidance for Industry[1]

Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance updates the final guidance *Guidance for Clinical Evaluation of Combination Estrogen/Progestin - Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women,* published in March 1995. The guidance is intended to provide recommendations to industry for studies of estrogen and estrogen/progestin drug products for the treatment of moderate to severe vasomotor symptoms associated with the menopause and moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. The guidance also addresses the reduction of the risk of endometrial hyperplasia or adenocarcinoma from estrogen exposure in postmenopausal women who have a uterus. For other indications, such as prevention of osteoporosis, sponsors are asked to direct inquiries to the appropriate CDER Office of New Drugs review division.[2]

II. BACKGROUND

Estrogen therapy has been used for over one-half century for the management of menopausal symptoms, including vulvar and vaginal atrophy and vasomotor symptoms. Since the early 1980s, estrogen has also been used to help prevent the loss of bone mineral density.

The use of estrogen alone (unopposed by progestin drugs) therapy in women who have a uterus is associated with an increased incidence of endometrial hyperplasia and adenocarcinoma of the endometrium. A regimen that combines a progestin drug with estrogen has been shown to

[1] This guidance was developed by the Division of Reproductive and Urologic Drug Products (DRUDP) in the Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA).

[2] Drugs for the prevention or treatment of osteoporosis are reviewed by the Division of Metabolic and Endocrine Drug Products, Office of New Drugs, CDER.

reduce the risk of estrogen-induced endometrial hyperplasia without compromising the positive effects of estrogen on vasomotor symptoms, vulvar and vaginal atrophy symptoms, or bone mineral density.

Although adding progestins to estrogens decreases the risk of endometrial hyperplasia in postmenopausal women, the addition of progestins to estrogen therapy may be associated with increases in the risk of a variety of serious adverse events, such as breast cancer, thromboembolic events, and myocardial infarction. Therefore, this guidance encourages sponsors to develop the lowest doses and exposures for both estrogens and progestins for indications sought, even though specific relationships between dose, exposure, and risk of adverse events may not be known. Sponsors are encouraged to investigate dosing schedules and drug delivery systems that can achieve efficacy with lowest possible exposures.

III. DRUG PRODUCTS CONTAINING ESTROGEN ALONE

A. Indications

There are two symptomatic indications for estrogen alone therapy.

1. Moderate to severe vasomotor symptoms associated with the menopause

Vasomotor symptoms in postmenopausal women are commonly known as *hot flushes or hot flashes*. The severity of vasomotor symptoms are defined clinically as follows:

Mild:	sensation of heat without sweating
Moderate:	sensation of heat with sweating, able to continue activity
Severe:	sensation of heat with sweating, causing cessation of activity

2. Moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause

Patient self-assessed symptoms of vulvar and vaginal atrophy include:

- Vaginal dryness (none, mild, moderate or severe)
- Vaginal and/or vulvar irritation/itching (none, mild, moderate or severe)
- Dysuria (none, mild, moderate or severe)
- Vaginal pain associated with sexual activity (none, mild, moderate or severe)
- Vaginal bleeding associated with sexual activity (presence vs. absence)

B. Study Considerations

The Agency recommends that prior to initiating phase 3 development, adequate dose ranging studies be conducted to identify the doses to be studied in the proof of efficacy studies. We recommend conducting one or more placebo-controlled trials to support efficacy of each indication in Section III.A. One adequately designed clinical trial to study both indications concurrently is possible. We recommend that studies be randomized, double-blinded and of 12-

week duration. In addition, we recommend that studies identify the lowest effective dose by including an ineffective dose as one of the doses evaluated.

If the drug product is considered to be a new molecular entity or poses an unexpected safety concern, two placebo-controlled phase 3 clinical trials are recommended to establish safety and efficacy.

C. Inclusion and Exclusion Criteria

We recommend that:

- Only postmenopausal women be included in studies. We define *postmenopausal* as 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.
- For the indication of treatment of moderate to severe vasomotor symptoms, study participants be enrolled who have a minimum of 7 to 8 moderate to severe hot flushes per day, or 50 to 60 per week at baseline.
- For the indication of treatment of moderate to severe symptoms of vulvar and vaginal atrophy, study participants be enrolled who have self-identified at least one moderate to severe symptom (see Section III.A.2) that is the most bothersome to her, have no greater than 5 percent superficial cells on a vaginal smear, and have a vaginal pH > 5.0.
- Study participants not be taking estrogen alone or estrogen/progestin containing drug products. The following washout periods are recommended before baseline assessments are made for subjects previously on estrogen alone or estrogen/progestin containing products:
  - — 1 week or longer for prior vaginal hormonal products (rings, creams, gels)
  - — 4 weeks or longer for prior transdermal estrogen alone or estrogen/progestin products
  - — 8 weeks or longer for prior oral estrogen and/or progestin therapy
  - — 8 weeks or longer for prior intrauterine progestin therapy
  - — 3 months or longer for prior progestin implants and estrogen alone injectable drug therapy
  - — 6 months or longer for prior estrogen pellet therapy or progestin injectable drug therapy
- Women >40 years have documentation of a negative screening mammogram (obtained at screening or within 9 months of study enrollment) and normal clinical breast examination prior to enrollment in clinical studies. Findings indicating any suspicion of breast malignancy would result in exclusion from enrollment.
- All subjects who have a uterus have endometrial biopsy performed at screening. Findings indicating endometrial hyperplasia or cancer would result in exclusion from enrollment.

D. Monitoring

We recommend that:

- All subjects who have a uterus undergo an endometrial biopsy at end-of-study.
- Any new findings noted during the conduct of the study or during the end-of-study physical examination (including findings related to the breast) receive careful and appropriate evaluation and be monitored until there is complete clinical resolution of any diagnosed condition.
- Sponsors provide plans for monitoring and/or reducing the risk of adverse endometrial effects in women who have a uterus.
- Safety assessments of lipids and of carbohydrate and coagulation parameters (antithrombin III, factor V Leiden, protein-C and protein-S) be conducted.
- Serum levels of the parent compounds and metabolites be measured.

E. Primary Endpoints

For the treatment of moderate to severe vasomotor symptoms, we recommend the following co-primary endpoints:

- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 4
- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 12
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 4
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 12

For the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, we recommend the following co-primary endpoints.

- Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her
- Mean change from baseline to week 12 in vaginal pH
- Mean change from baseline to week 12 in vaginal maturation index (parabasal and superficial cells)

F. Study Analysis

For estrogen alone products intended to treat moderate to severe vasomotor symptoms, we recommend that the primary efficacy analyses show a clinically and a statistically significant

reduction, within 4 weeks of initiation of treatment and maintained throughout 12 weeks of treatment, in both the frequency and severity of hot flushes in the treated groups compared with the control groups. Subjective measures (e.g., daily patient diary entries) can be used as primary efficacy endpoints. Alternatively, objective measures (e.g., thermography) can be used both as primary efficacy endpoints and as validation of subjective endpoints. We recommend that study results clearly identify the lowest effective dose of estrogen to support the indication by demonstrating an ineffective lower dose.

For estrogen alone drug products intended to treat moderate to severe symptoms of vulvar and vaginal atrophy, we recommend that the primary efficacy analyses demonstrate a statistically significant improvement versus placebo from baseline to week 12 of treatment in all three of the following parameters:

1. Maturation Index (decrease of parabasal vaginal cells and increase in superficial vaginal cells)
2. Lowering of the vaginal pH
3. The moderate to severe symptom identified by the subject as being most bothersome to her

IV. DRUG PRODUCTS CONTAINING ESTROGEN PLUS PROGESTIN

The approval of specific fixed dose estrogen/progestin drug products for estrogen class labeling indications in women who have a uterus will be based on two criteria: (1) that each component contribute to the efficacy and safety as defined in the combination drug policy (see 21 CFR 300.50) and (2) the determination that a combination drug contains the lowest effective dose of each of its active components for their respective labeled indications.

A. Indications

1. Estrogen Component

The symptomatic indications for estrogen/progestin therapy are the same as those previously discussed under Section III.A of this guidance.

2. Progestin Component

The progestin component is added to estrogen alone regimens for safety purposes to oppose the adverse effects of estrogen on the endometrium in women who have a uterus. We recommend that sponsors propose low-dose combination estrogen/progestin regimens and dosing schedules that demonstrate endometrial safety and have acceptable endometrial bleeding profiles.

B. Study Considerations

To support the indication of the treatment of moderate to severe vasomotor symptoms or the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, see Section III.B in this guidance.

To demonstrate protection of the endometrium, we recommend that a single, 12-month, randomized, double-blind, dose-ranging phase 3 clinical trial be conducted and include two or more progestin drug treatment arms for each estrogen dose studied. However, the indications in Section III.A can be studied as part of the 12-month endometrial protection study, provided all entrance criteria for each indication are met and the study is powered adequately for each endpoint. We recommend that study results clearly identify the lowest effective dose of estrogen (as described in Section III.B) and the lowest effective dose of progestin to support endometrial safety by demonstrating an ineffective lower dose on the endometrium.

If the drug to be studied is considered to be a new molecular entity or if it poses unique safety concerns, two placebo-controlled phase 3 clinical trials are recommended to establish safety and efficacy.

C. Inclusion and Exclusion Criteria

Please refer to the criteria set out in Section III.C., except as specified below.

We recommend that:

- All subjects have a uterus and have an evaluable screening endometrial biopsy (i.e., endometrial tissue sufficient for diagnosis). Findings indicating endometrial hyperplasia or cancer would result in exclusion from enrollment and subjects would be referred for *standard of care* clinical management.
- A negative screening mammogram (obtained at screening or within 3 months of study enrollment) and normal clinical breast examination be documented prior to enrollment in clinical studies for women > 40 years old. Findings indicating any suspicion of breast malignancy would result in exclusion from enrollment.

D. Monitoring

We recommend that:

- The endometrial tissue obtained by endometrial biopsy at screening, during the conduct of the study, and at the end-of-study be processed in the same manner by a central laboratory.
- Endometrial biopsies and not uterine ultrasounds be used for the evaluation of endometrial hyperplasia (sponsors interested in establishing a correlation between transvaginal ultrasound and endometrial biopsy results may perform transvaginal ultrasound immediately preceding endometrial biopsies).
- A single pathologist reader (any one of the three blinded pathologists) initially assess the slides from the endometrial biopsies obtained at screening or because of participant bleeding while on study drug (safety reading).

- For the efficacy evaluation, three independent expert pathologists, blinded to treatment group and to each other's readings, determine the diagnosis for endometrial biopsy slides during the conduct of the study.
- Curricula vitae for participating pathologists be provided to the FDA and document expertise in gynecologic pathology.
- Participating study pathologists be from different institutions with independent fiduciary and organizational reporting, and these pathologists not meet to review slides before or during the conduct of the clinical trial.
- Standardized criteria as provided in Blaustein's pathology text (Pathology of the Female Genital Tract) be used for the diagnosis of endometrial hyperplasia (see Appendix for recommended histologic characteristics of the endometrium).
- Endometrial polyps be fully characterized as to the glandular proliferation and atypia (see Appendix for additional histologic characteristics of the specimen).
- Subjects found to have endometrial hyperplasia or adenocarcinoma of the endometrium be excluded from further drug treatment (if discovered during study drug treatment period) and referred for *standard of care* clinical management and followed to complete resolution, and the report of any medical or surgical procedures and the resultant pathology be provided to the FDA.
- If hyperplasia is diagnosed by the single safety reader for a subject who has bled while on study drug, this diagnosis be maintained for the efficacy evaluation and the slides become part of the slide set given to the two other pathologists for reading.
- For the efficacy evaluation, the concurrence of two of the three pathologists be accepted as the final diagnosis. If there is no agreement among the three pathologists, the most severe pathologic diagnosis (i.e., atypical hyperplasia > complex hyperplasia > simple hyperplasia > benign endometrium) would be used as the final diagnosis.
- The slide set distributed to each of the three pathologists for the end-of-study pathology review incorporate control sides representing a randomly selected 10 percent of the screening normal slides and all slides from subjects excluded for the diagnosis of hyperplasia or cancer to insure quality control.
- Digital recording of diagnostic areas of the slides be maintained by the central laboratory and be made available upon FDA request.
- Any new findings noted during the conduct of the study and on end-of-study physical examination (including findings related to the breast) receive careful and appropriate evaluation and be monitored until there is complete clinical resolution of any diagnosed condition.
- Safety assessments of lipids and of carbohydrate and coagulation parameters (antithrombin III, factor V Leiden, protein-C and protein-S) be conducted.
- Serum levels of the parent compounds and metabolites be measured.

E. Primary Endpoints

For protection of the endometrium, we recommend the evaluation of the incidence rate of endometrial hyperplasia at 12 months.

F. Study Analysis

See Section III.F. for analysis of primary endpoints for treatment of moderate or severe vasomotor symptoms or moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. The objective of the clinical trial is to demonstrate the lowest effective dose of the progestin drug that reduces the estimated risk of endometrial hyperplasia after 1 year of estrogen/progestin treatment. The reported 1-year background incidence rate for endometrial hyperplasia in postmenopausal women and in postmenopausal women treated with currently marketed combination estrogen/progestin drugs is approximately 0-1 percent. We recommend that the results from the clinical trial demonstrate a hyperplasia rate that is ≤ 1 percent with an upper bound of the one-sided 95 percent confidence interval for that rate that does not exceed 4 percent. The frequency of atypical hyperplasia and cancer are important additional factors to be considered in determining approvability of the drug product. The incidence of hyperplastic polyps and associated atypia would be considered in the safety review.

APPENDIX: HISTOLOGIC DESCRIPTIONS RECOMMENDED FOR USE WHEN READING ENDOMETRIAL BIOPSY SLIDES

Histologic Characteristics of the Endometrium

0. No tissue

1. Tissue insufficient for diagnosis

2. Atrophic

3. Inactive

4. Proliferative

    a. Weakly proliferative

    b. Active proliferative

    c. Disordered proliferative

5. Secretory

    a. Cyclic type

    b. Progestational type (including stromal decidualization)

6. Menstrual type

7. Simple hyperplasia without atypia

8. Simple hyperplasia with atypia

9. Complex hyperplasia without atypia

10. Complex hyperplasia with atypia

11. Carcinoma (specify type)

Additional Histologic Characteristics

If there are any polyps, please specify the type or types.

- Functional
- Atrophic
- Hyperplastic without atypia
- Hyperplastic with atypia
- Carcinomatous

If there is any stromal tissue, please specify the type or types.

- Smooth muscle tissue, normal
- Features suggestive of adenomyoma
- Features suggestive of stromal nodule
- Sarcoma (specify type)

If there is any metaplasia, please specify the type or types.

- Squamous
- Papillary
- Eosinophilic
- Ciliated
- Mucinous
- Syncytial
- Other type (specify type)

If there is any cervical tissue, please specify the type or types.

- Fragments of negative cervical epithelium
- Endocervical polyp
- Atypical endocervical glandular epithelium
- Atypical squamous metaplasia
- Squamous dysplasia
- Cervical carcinoma

Table 9-3: Schedule of Events

				Titration Week	Stable Dosing Weeks					
Procedures Visit window	Screening[a]	Baseline[a]	Randomization +2 days	(Treatment Week 1) +2 days	SDW 4 (Treatment Week 5) ±2 days	SDW 8 (Treatment Week 9) ±2 days	SDW 12 (Treatment Week 13) –3days	SDW 18 (Treatment Week 19) ±2 days	SDW 24 (Treatment Week 25) –3 days	Follow-up[b] (phone call)
Informed consent	X									
Medical/Medication history	X									
Physical examination	X								X	
Vital signs	X		X	X	X	X	X	X	X	
Height	X									
Weight	X						X		X	
Laboratory tests	X								X	
Washout (as required)	X									
DiaryPRO dispensed		X								
Diary uploaded at site			X	X	X	X	X	X	X	
DiaryPRO returned to patients			X	X	X	X	X	X		
Medication dispensed[c]			X		X		X	X		
Blister cards returned to site					X	X	X	X	X	
CGIC/PGIC							X[d]		X[d]	
MENQOL and PSQI			X		X		X		X	
Adverse events		X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X

Abbreviations: CGIC, Clinical Global Impression of Change; MENQOL, Menopause-Specific Quality of Life Questionnaire; PGIC, Patient Global Impression of Change; PSQI, Pittsburgh Sleep Quality Index; SDW, stable dosing week.
a The screening visit occurred at the beginning of baseline week and the baseline visit occurred at the end of the baseline week.
b Occurred at Week 26 for patients who completed the study.
c Study drug was provided in blister packs containing the appropriate number of tablets for each day of the study, separated into morning and evening doses for treatment during Titration through SDW 24. Patients were instructed to take the designated study drug by mouth in the morning with breakfast and in the evening with dinner. The first dose was given on the evening of the randomization visit (Day 1).
d Completed before all other procedures.

Table 9–3: Schedule of Events

				Titration Week	Stable Dosing Weeks (SDWs)			
Procedures Visit window	Screening[a]	Baseline[a]	Randomization +2 days	(Treatment Week 1) +2 days	SDW 4 (Treatment Week 5) ±2 days	SDW 8 (Treatment Week 9) ±2 days	SDW 12 (Treatment Week 13) –3 days	Follow-up[b] (Phone Call)
Informed consent	X							
Medical/Medication history	X							
Physical examination	X						X	
Vital signs	X		X	X	X	X	X	
Height	X							
Weight	X						X	
Laboratory tests	X						X	
Washout (as required)	X							
DiaryPRO dispensed		X						
Diary uploaded at site			X	X	X	X	X	
DiaryPRO returned to patients			X	X	X	X		
Study drug dispensed[c]			X		X			
Blister cards returned to site					X	X	X	
CGIC/PGIC							X[d]	
MENQOL and UQOL			X		X		X	
PSQI			X		X		X	
Adverse events		X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X

Abbreviations: CGIC, Clinical Global Impression of Change; MENQOL, Menopause-Specific Quality of Life Questionnaire; PGIC, Patient Global Impression of Change; PSQI, Pittsburgh Sleep Quality Index; SDW, stable dosing week; UQOL, Utian Quality of Life Questionnaire.

[a] The screening visit occurred at the beginning of baseline week and the baseline visit occurred at the end of the baseline week.

[b] Occurred at Week 14 for patients who completed the study.

[c] Study drug was provided in blister packs containing the appropriate number of tablets for each day of the study, separated into morning and evening doses

Table 9-3: Schedule of Events

				Efficacy Treatment Period						
Procedures Visit window	[a]Screening	2-week Baseline Period	[b]Randomization +2 days	Week 4 ±2 days	Week 8 (phone) ±2 days	Week 12 –3 days	Week 16 (phone) ±2 days	Week 20 ±2 days	Week 24 /Early Termination –3 days	Week 28 Follow-up –7 days
Informed consent	X									
Medical/Medication history	X									
Physical examination	X								X	
Vital signs	X		X	X		X		X	X	
Height	X									
Weight	X								X	
Laboratory tests[c]	X								X	
Washout (as required)	X									
mPRO dispensed		X[d]								
mPRO reviewed by center		X	X[e]	X	X	X	X	X	X	
Medication dispensed[f]			X			X				
Blister cards returned to center				X		X		X	X	
CGIC/PGIC						X[g]			X[g]	
MENQOL and ISI			X	X		X			X	
C-SSRS	X			X		X			X	X
Adverse events		X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; AM, morning; CGIC, Clinical Global Impression of Change; C-SSRS, Columbia-Suicide Severity Rating Scale; ISI, Insomnia Severity Index; MENQOL, Menopause-Specific Quality of Life Questionnaire; PGIC, Patient Global Impression of Change; PM, evening.
a Screening and any required drug washout could take up to 12 weeks.
b At the end of Randomization, patients were to start the 1-week (up to 12 days if AEs occurred) titration period, as Week 1 of study dosing.
c Includes chemistry, hematology, and follicle stimulating hormone (Screening only).
d The e-diary mPRO was dispensed at the start of the 2-week Baseline period.
e The e-diary mPRO was reviewed at the end of the 2-week Baseline period.
f Provided in blister packs of tablets for each study day (morning and evening doses) for Weeks 1 to 12 (at Randomization) and Weeks 13 to 24 (at Week 12), as 2 separate kits. Patients were instructed to take the study drug by mouth (in the morning with breakfast, in the evening with dinner). The first dose was given PM at the Randomization Visit (Day 1).
g Completed before all other procedures.